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INSULIN

MEDICINE MONOGRAPHS

VOLUME VI

INSULIN

ITS USE IN THE TREATMENT OF DIABETES

PART I—PHYSIOLOGY

BY

J. J. R. MACLEOD

PART II—CLINICAL SECTION

BY

W. R. CAMPBELL

Departments of Medicine and Physiotherapy
University of Toronto

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PREFACE

Since it became available, insulin has proved to be of inestimable value in the treatment of diabetes. Not only has it reduced the mortality from this disease but, by its use combined with intelligent regulation of the diet, the efficiency and the sense of well-being of the patient can be restored practically to normal and life again made reasonably tolerable. But no hard and fast rules of treatment that are applicable to all cases can be laid down; each one must be studied by itself and the treatment, by dietary regulation and the use of insulin, adapted to its specific needs.

To assist the physician in this method of treatment it is hoped that the present volume may prove of value. It contains a review, based on experience, of the general principles that should guide the physician in formulating his own plan of treatment, including practical directions in the use of dietetic measures in treatment.

The first few chapters are devoted to an account of those aspects of the experimental work with insulin which have a direct bearing on its clinical application, and these are added since in diabetes, probably more than in any other disease of metabolism, investigation on laboratory animals has formed the basis of treatment in man. As a guide to those who may wish to follow the subject further, and thereby add to the sum of knowledge, a comprehensive bibliography has been added.

The authors beg to acknowledge the kindness of the Editor of the Canadian Medical Association Journal in permitting them to reprint much of the material now contained in Chapter XIII. Thanks are also due to Miss Mame T. Porter for permission to use numerous tested recipes and tables developed during the treatment of diabetic patients in the Toronto General Hospital.

W. R. C.
J. J. R. M.

Toronto, July, 1925

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A folder entitled "General Directions for Diabetic Treatment with Condensed Diabetic Diet Lists," accompanies each copy of this book.

Additional copies of the folder may be obtained from the publisher in lots of five for $1.00; in lots of 50 copies, $5.00. Single copies are not sold. Order from The Williams & Wilkins Company, Baltimore, Maryland.

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PART I—PHYSIOLOGY

J. J. R. MACLEOD

CHAPTER I

Introduction

As an outcome of the well-known discovery of von Mering and Minkowski (1) (1889) that pancreatectomy results in complete diabetes, it came generally to be assumed that the pancreas must produce an internal secretion, or hormone, having the function of controlling the metabolism of the carbohydrates in the animal body. The observations (Diamare (2), Laguesse (3), etc.) that the peculiar islets of cells that had previously been described by Langerhans (4) (1869) occur in, or are associated with, the pancreas in all vertebrates, coupled with the demonstration by Ssobolew (5) and Schulze (6) (1900) that they do not undergo destruction after ligation of the ducts or in grafts of the gland—in neither of which conditions diabetes occurs—indicated that this anti-diabetic hormone must be derived from the islets. The name insulin was, therefore, suggested for it by Sir E. Sharpey Schafer (7) (1916).

Attempts to isolate insulin in extracts of pancreas were at first of no avail, although they almost succeeded in 1908. In this year Zuelzer (8) prepared from the pancreas of recently fed animals an alcoholic extract, which on intravenous injection, was capable of greatly diminishing (in several animals) the glycosuria resulting from injections of epinephrin and (in 1 animal), from pancreatectomy. An hour or so prior to killing the animals, from the pancreas of which the extract was to be prepared, the veins of the gland were tied so as to cause congestion, the object being, apparently, that the hormone might accumulate. The extracts contained considerable amounts of protein. Zuelzer subsequently administered portions of his extract to 8 patients suffering from diabetes mellitus and found that the glycosuria was greatly diminished in intensity and that the ketone bodies usually disappeared from the urine. Several of the patients improved in their general condition but as a rule considerable

degrees of fever temporarily followed the injections. Although the extract was usually given intravenously it was observed that its effects on the glycosuria did not develop until the second or third day following the injection, and that they persisted for several days. Forschbach (9) confirmed Zuelzer's findings on depancreatized dogs but considered that the alleviation of the symptoms in diabetic patients was due to the febrile reaction which followed the injections, rather than to a specific action of an antidiabetic hormone. Further attempts to use Zuelzer's extracts in the treatment of diabetes were abandoned.

The next attempt to demonstrate the presence of insulin was that of Knowlton and Starling (10) in 1911. Extracts were made from pancreas with weak acid following the procedure used for preparing secretin, and they were tested by observing their effect on the rate of disappearance of sugar from the fluid perfused through the surviving mammalian heart. In several of the experiments the extracts caused the sugar to disappear more rapidly from the perfusion fluid, but investigation of the behavior of the glycogen in the heart, in subsequent experiments of a similar nature, induced Starling (10) to consider the results with extracts unreliable, and further work in this direction was abandoned by him. This research is, however, important because it pointed a new way to the testing of the extracts, and in 1916 Clark (11) succeeded in showing that the sugar consumption by the excised mammalian heart is definitely increased when the Locke's solution has first of all been passed through the blood vessels of the pancreas. The results of this investigation demonstrated that the pancreas produces an internal secretion which is capable of influencing the rate at which the heart removes sugar from the fluid perfused through it. Clark later showed that, although no change occurs in the percentage of sugar contained in the Locke's solution by perfusing it through the pancreas, as determined by the ordinary reduction methods, the sugar does become altered in some way, as revealed by examination of the polarizing power of the solution. It cannot be said, however, that the changes observed were of sufficient magnitude to make this certain.

Reference must also be made to the investigations of Gley (13)

(1905), Rennie and Fraser (12) (1907), E. L. Scott (14) (1911), J. R. Murlin and Kramer (15) (1913), I. Kleiner (16) (1919) and Paulesco (17) (1921). All of these investigators, using various methods both for preparing the extracts and for testing their possible antidiabetic properties, were able to secure results which, though unconvincing were, nevertheless, of such a nature as to keep alive the hope that some day it would be possible to obtain satisfactory pancreatic extracts containing insulin. Gley's investigations were made in 1905 but were not published at that time, a sealed statement of them being deposited with the Société de Biologie. This was published in 1922 (13a) following the first announcement of the Toronto researches. Following the method used by Claude Bernard, Gley caused degeneration of the pancreas by injecting the ducts with oil. Even after the gland had become replaced by fibrous tissue the animals did not become diabetic but an extract of the sclerosed mass, when injected intravenously into a depancreatized dog, caused reduction in the glycosuria and a decided alteration of the diabetic symptoms. Rennie and Fraser took advantage of the fact, first discovered by Diamare, and further developed by Laguesse and by Rennie, that the islet tissue in certain of the bony fishes (Teleostei) is isolated from the main zymogenous tissue of the pancreas and exists as relatively large glands situated in the mesentery, usually near the gall bladder. The administration of extracts of these "principal islets," by mouth, did not definitely improve the clinical symptoms of diabetes, though, in one case, subcutaneous injection did appear to reduce the glycosuria and to improve the general condition of the patient. This method of administration was not further attempted because toxic symptoms followed the injections. E. L. Scott, acting upon Ssobolew's suggestion, prepared extracts from the pancreas after attempting to cause atrophy of the acinous tissue by ligation of the ducts, but he discontinued the observations because he found that complete atrophy of the acinous tissue did not occur. He then tried alcoholic and acidulated watery extracts of the intact gland, the object in all his methods being to circumvent the destructive action of the digestive enzymes. He found, particularly with acidulated watery extracts, that intravenous injection into diabetic dogs reduced the

glycosuria temporarily and seemed to improve the general condition of the animals. A slight rise in body temperature was considered by Scott to be a possible factor in accounting for the decreased glycosuria. Murlin and Kramer prepared extracts from the pancreas (dogs or cattle) either with acidified Ringer's solution, or with weak alkali. They tested the immediate and remote effects following subcutaneous injection of the extracts into diabetic dogs and they observed the behavior of the respiratory quotient along with the degree of glycosuria—and, in some cases, of hyperglycemia—to ascertain whether or not an antidiabetic hormone was present. Sometimes these workers combined the extracts of pancreas with extracts of duodenum, thinking that the secretion present in the latter might activate the antidiabetic hormone. Many of the results show evidence of the presence of insulin in the extracts, particularly certain of those in which the respiratory quotient was examined. Unfortunately, the observers failed to interpret their results correctly, being confused by the possibility that the alkali present in the extracts might in itself account for most of the beneficial results. Their conclusion "after some three years' intermittent occupation with the problem" was "that in the totally depancreatized dog in good condition, i.e., not moribund, the alkali alone is almost always without effect on the respiratory metabolism. . . . . With the partially operated animal, however, the result is striking and immediate. . . . . We have obtained some evidence also, that pancreatic material . . . . is, when administered with alkali, of distinct benefit to the diabetic organism."

In collaboration with Clough, Stokes, Gibbs and Stone, Murlin (18) has more recently repeated Clark's experiments of perfusion of the blood vessels of the pancreas, using a variety of perfusates, such as weak alkaline, or acid or glucose solutions. Considerable quantities of insulin were found to pass into the perfusion fluids, particularly when the latter were acid in reaction. The antidiabetic properties were tested by various methods and in one case the life of a depancreatized dog was prolonged to thirty days by injecting perfusates in seven doses.

Kleiner, continuing work which he had previously done with

Meltzer, studied the influence of pancreatic extracts on the degree and duration of the hyperglycemia which follows injection of glucose into depancreatized dogs. The extracts were made with water and were unfiltered. After being diluted with isotonic saline they were administered intravenously at a slow rate. Decided reduction in the hyperglycemia was demonstrated to occur and it was shown by suitable controls that dilution of the blood was not responsible for the result.

Paulesco allowed minced pancreas to stand for twenty-four hours with distilled water in the ice box and the resulting extract, though rich in protein, was found to cause the blood sugar to become reduced from 0.16 to 0.037 per cent in a depancreatized dog, the sugar also disappearing from the urine. He did not, however, follow up this result either by studying the effect of the extracts on the other symptoms of diabetes or by preparing extracts suitable for use in human patients.

There could be little doubt as to the existence of insulin in the pancreas, the problem—and for practical reasons a most important one—was to devise means for extracting it in a condition suitable for continued administration to diabetic patients. With this object in view F. G. Banting (19) undertook to prepare extracts from pancreas that had been caused to undergo partial degeneration by ligation of the ducts. Since it was known that the acinous tissue, from which the digestive ferments are derived, undergoes degeneration more rapidly than the islets which are presumably the source of insulin, it was hoped that in this way active extracts could be obtained. With the assistance of C. H. Best, the antidiabetic properties of the extracts were tested by injecting them into depancreatized dogs and observing the effects produced on the hyperglycemia and glycosuria. The results of a typical experiment on a dog that was depancreatized on August 11 (1921) are shown in figure 1. An extract, made by ice-cold Ringer's solution from the degenerated pancreas (ten weeks after ligation of the ducts) of another dog, was given intravenously six hours after the operation. This prevented the blood sugar from rising above 0.20 per cent until 10:00 p.m. on August 12 when it reached 0.3 per cent. The amounts of extract injected were

then increased with the result that the blood sugar declined, reaching a little below 0.10 per cent in the forenoon of August 13. After this, similarly prepared extract from the degenerated gland of another dog was used, and on August 14 an isolated large injection resulted in a fall of blood sugar from 0.175 per cent to nearly 0.09 per cent. Meanwhile very little sugar was being excreted by the urine, but as the effect of the last injection of extract wore off the amount rose rapidly and on August 15 reached 16 grams, the blood sugar now standing at

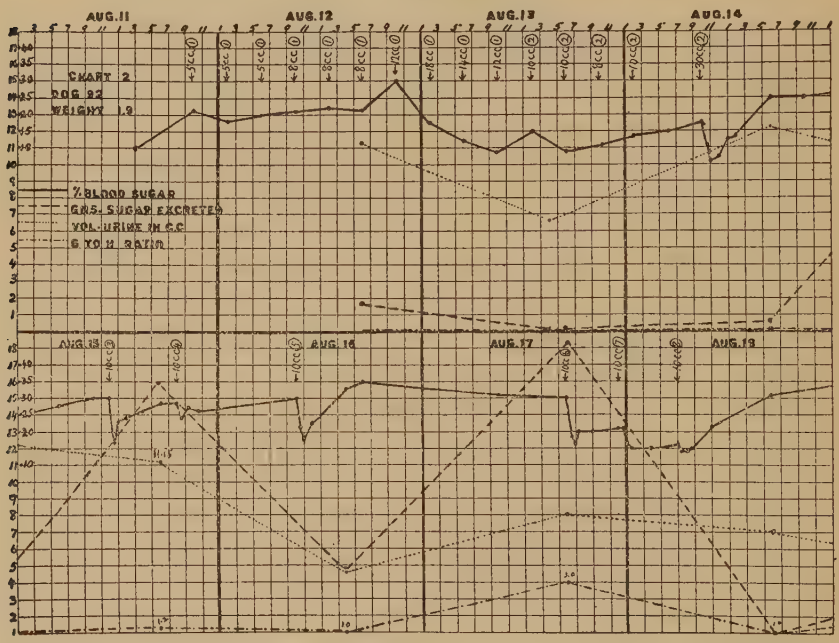


FIG. 1. CURVES OF PERCENTAGE OF BLOOD SUGAR, ETC., IN DEPANCREATIZED DOGS, AS AFFECTED BY INJECTIONS OF EXTRACTS OF PARTIALLY DEGENERATED PANCREAS

The numbers in circles refer to the nature of the extracts as follows: (1) Degenerated pancreas, dog 394. (2) Degenerated pancreas, dog 390. (3) Degenerated pancreas in 0.1 per cent HCl. (4) Degenerated pancreas in 0.10 per cent NaOH. (5) Degenerated pancreas in 0.1 per cent HCl. (6) Whole gland extract, fresh, cold. (7) Whole gland extract in 0.1 per cent HCl. (8) Whole gland extract in 0.1 per cent NaOH. Dog died August 30. The first column of figures along ordinates refers to all the curves except that of the percentages of blood sugar which are given in figures of the second column. In the case of "volume of urine" the figures are to be multiplied by 100.

0.30 per cent. Injections of extract prepared by weak acid from degenerated pancreas on August 15 and 16 caused prompt reductions in blood sugar, and the urinary sugar again declined to about 5 grams. There could be no doubt that the extracts of degenerated pancreas had reduced the severity of the diabetic symptoms, and on August 17 and 18 extracts from normal (dog) pancreas were tried with similar beneficial results, as judged by both the hyperglycemia and the glycosuria. The observations were continued on this animal until August 22, one of the extracts used with successful results being prepared from a pancreas after exhaustion of the acini by continued injections with secretin. After this date, as a result of discontinuance of the injections the blood sugar rose to between 0.30 and 0.35 per cent, at which it remained until August 26, the daily urinary sugar varying between 6 and 13 grams. The animal died on August 30 and at autopsy no trace of pancreas was found by naked eye examination. In other experiments, in which extracts prepared by similar methods from other tissues than the pancreas were used, no changes were observed in the blood sugar, showing that insulin is almost, if not exclusively, derived from this gland. Administration *per rectum* was without effect. In certain of the experiments glucose solutions were injected and it was found that when this was accompanied by the extract, decidedly less than the expected amount of glucose reappeared in the urine. Thus, in one experiment without extract the excretion of glucose during four hours following the injection of 10 grams was 9.94 grams, whereas on the next day when this amount was injected along with extract it was only 4.4 grams. Hemoglobin determinations showed that the changes in the percentage of blood sugar were not due to dilution of the blood.

Observations of a similar type were made on 9 other depancreatized dogs, partly in order to make certain that no fortuitous circumstances could be held responsible for the results, and partly in the endeavor to obtain more satisfactory figures for the sugar excretion by the urine.

No attempt was made at this stage to investigate the possible effects of the extracts on other symptoms of diabetes, such as glycogen formation or ketosis, since, with the limited quantities of extract that were then available, it was considered more important to

devote attention first of all to finding methods for the preparation of larger supplies, using the behavior of the blood and urinary sugar of diabetic dogs to determine their antidiabetic potency.

As the next step towards obtaining larger amounts of extract the pancreas of fetal calves of under four months development was used by Banting and Best (22), since it had been shown by Ibrahim (20) that at this stage the acini of the pancreas are insufficiently developed to produce active proteolytic enzymes, whereas the islets are plentiful and are apparently capable of supplying sufficient internal secretion of insulin to minimize greatly the severity of glycosuria in the mother (Carlson and Drennan (21)). These extracts were made partly with Ringer's solution and partly with alcohol. In the latter procedure, the alcohol was removed by evaporation in a current of warmed air and the residue redissolved in Ringer's solution. Intravenous or subcutaneous injections into depancreatized dogs reduced the hyperglycemia and glycosuria. This result encouraged Banting and Best (22) to see whether potent extracts could be obtained from the pancreas of full grown cattle by extraction with equal volumes of 95 per cent alcohol made slightly acid with HCl. This extractive was used with the object of minimizing the destructive action of the proteolytic enzymes, and its possible value in this connection, previously recognized by Zuelzer and E. L. Scott, had been in mind from the very start of the investigations. After the removal of the alcohol by warmed air and of excess of fat by toluene, the extracts were found to possess strong antidiabetic properties, and it was now possible to show without doubt that by continuous injections a great improvement occurred in the general condition of the animals, one of which lived for seventy days, when it was killed by chloroform. On gross examination no trace of the pancreas could be found but serial sections of the duodenum, made by Dr. W. L. Robinson, revealed the presence in the submucous coat, near the entry of the main pancreatic duct, of a small nodule in which, however, no islets could be seen. The possibility must always be borne in mind that these duodenal nodules of pancreatic tissue which have been found by Fisher and by us in other depancreatized dogs kept alive by insulin may be embryonic rests which have become

hypertrophied as a result of the removal of the main gland. They are probably always related to the ducts and their occurrence suggests the possibility that a certain restoration of the lost pancreatic function may occur in depancreatized animals.

An endeavor was now made to purify the alcoholic extracts of adult pancreas sufficiently for trial on a diabetic patient. The alcohol was removed by warmed air or *in vacuo* at a low temperature, the excess of fat extracted by toluene and the watery residue, now reduced to one-fifth the original volume, was passed through a Berkefeld filter. The resulting extract, injected into a diabetic patient (a boy aged fourteen years), reduced the blood sugar by a little over 25 per cent, and somewhat diminished the glycosuria, but "owing to the high percentage of protein . . . . sterile abscesses formed in a few instances at the site of injection." Banting and Best (23) stated that the potency of these extracts is destroyed by heat and by digestion with trypsin and that the active principle is insoluble in 95 per cent alcohol.

CHAPTER II

Methods of Preparation of Insulin

Before further attempts could be made to investigate the possible therapeutic value of the extracts it was necessary to remove from them the irritating substances responsible for abscess formation, and to demonstrate in diabetic dogs that not only are the hyperglycemia and glycosuria reduced by their action, but the other diabetic symptoms as well. At the same time it was considered important to see whether other forms of experimental hyperglycemia, such as that caused in rabbits by piqûre or epinephrin, would be affected by the extracts. The problem of purification of the extract was entrusted to J. B. Collip (24) who, as a first step in his work, injected some of the crude extract into normal rabbits and found the blood sugar to become reduced. This furnished him with a method for testing the potency of the various precipitates and filtrates into which the crude alcoholic extracts could be fractionated by various strengths of alcohol. He finally found that the active principle remained in solution in alcohol up to a percentage of about 92 and that by using percentages somewhat below this, much of the protein could be removed from the extracts by precipitation. His finally evolved method was as follows:

To a small volume of 95 per cent ethyl alcohol freshly minced pancreas was added in equal amount. The mixture was allowed to stand for a few hours with occasional shaking. It was then strained through cheese cloth and the liquid portion at once filtered. The filtrate was treated with two volumes of 95 per cent ethyl alcohol. It was found by this treatment that the major part of the protein was removed while the active principle remained in alcoholic solution. After allowing some hours for the protein precipitation to be effected the mixture was filtered and the filtrate concentrated to small bulk by distillation *in vacuo* at a low temperature (18° to 30°C.). The lipoid substances were then removed by twice extracting

with sulphuric ether in a separating funnel and the watery solution returned to the vacuum still, where it was further concentrated till it was of a pasty consistency after which 80 per cent ethyl alcohol was added and the mixture centrifuged. After centrifuging, four distinct layers were manifested in the tube. The uppermost was perfectly clear and consisted of alcohol holding all the active principle in solution. Below this, in order, were a flocculent layer of protein, a second clear watery layer saturated with salt and a lowermost layer consisting of crystals of salt. The alcohol layer was removed by means of a pipette and was at once delivered into several volumes of 95 per cent alcohol, or better, of absolute alcohol. It was found that this final treatment with alcohol of high grade caused the precipitation of the active principle along with adherent substances. Some hours after this final precipitation the precipitate was caught on a Buchner funnel, dissolved in distilled water and then concentrated to the desired degree by use of the vacuum still. It was finally passed through a Berkefeld filter.

Various *methods* have been devised to purify further the insulin prepared by Collip's method and as a result preparations giving only a faint biuret test have been obtained. The best known methods are those of Doisy, Somogyi and Shaffer (25), and of Dudley (26). In the former, the acidified alcoholic extract of pancreas, after removal of the alcohol, is mixed in faintly acid reaction with ammonium sulphate in the proportion of 40 grams to each 100 cc. of solution. After standing in a separating funnel the precipitate rises to the surface so that the underlying fluid can readily be run off. When all possible liquid has been removed the precipitate is shaken with alcohol in such proportion as to give about 70 to 75 per cent, and the mixture is centrifuged. A clear alcoholic solution separates which is pipetted off and the concentration of alcohol in it raised to about 90 per cent, the reaction being carefully adjusted to a pH of between 5 and 6. After standing some hours, the precipitate which forms is collected and redissolved in water containing traces of acid (or alkali). Precipitation is again effected by bringing pH back to between 5 and 6, and this process of precipitation and resolution is repeated several times, the final precipitate being collected on a filter and dried in a vacuum desiccator. It will be seen that this method depends mainly on precipitation at the isoelectric point.

It is one which is being used successfully on a large scale and it yields insulin which is practically free from toxic or irritating qualities and possesses remarkable keeping qualities. Its discoverers have generously allowed it to be used for large scale production.

In the Dudley process crude insulin prepared by Collip's process is dissolved in a small quantity of water and the solution centrifuged to free it from insoluble material. The clear supernatant solution is diluted with water to bring the concentration of insulin to about 1.5 per cent. An equal volume of a saturated watery solution of picric acid is added and the material, contained in a tall vessel, is allowed to stand some days so that the precipitate may settle. The clear supernatant fluid is decanted and the precipitate dissolved in a minimum of water containing weak Na_2CO_3. If all does not dissolve the solution is centrifuged. Acid is added to the clear solution in an amount sufficient to neutralize the Na_2CO_3 as a result of which the insulin picrate is reprecipitated. To ensure complete reprecipitation one-half the volume of saturated picric acid solution is added to the solution. After standing some days the precipitate is collected on a Buchner funnel and thoroughly washed with weak picric acid solution (5 cc. saturated picric acid in 100 cc. water) after which it is transferred to a beaker and stirred with a solution of HCl in 75 per cent alcohol in the proportion of about 15 cc. per gram of moist picrate taken (24 cc. 3 *N* HCl in 75 cc. absolute alcohol). "The picrate after first forming thick dark brown oily drops dissolves in this reagent yielding a somewhat turbid dark yellow liquid." About ten volumes of acetone are then added to precipitate the hydrochloride which is collected on a filter, washed with acetone, and finally, with dry ether. It is then dried in a vacuum desiccator.

In the preparation there are two stages during which loss of insulin is liable to occur; one of these is prior to placing the minced gland in acidified alcohol and the other, in the watery extract after removal of the alcohol. In order to minimize the losses in the early stages Krogh and Widmark (27) place the pancreas, after removal from the animal, in a freezing mixture of ice and 2 per cent saline solution in which it is brought to the laboratory. It is then frozen solid and the blocks of ice cut by rapidly revolving knives into thin shavings which

are collected in acidified alcohol. After extraction and removal of the alcohol, the extract is tested as to stability of insulin by roughly assaying it before and after incubation for twenty-four hours in neutral reaction. If it is found to be satisfactorily stable the insulin is further purified by the ammonium sulphate method of Doisy, etc. The yields by this method are remarkably high, probably because of the great care that is taken to chill the pancreas to freezing point as early as possible after killing and to break up thoroughly the frozen gland so that extraction is thorough. We have frequently noted when working with the principal islets of bony fishes (cod, angler fish, sculpin, etc.) that the yields of insulin are greatly increased when the glands are frozen solid immediately after removal and we have attributed this, not only to the inhibition of proteolytic digestion, but also to the tearing up of the islet cells by the large ice crystals which form under these conditions.

Brailsford Robertson and Anderson (28) employ sodium sulphate to remove water from the initial alcoholic extracts, thus effecting considerable saving in alcohol. This action depends on the fact that exsiccated Na_2SO_4 when mixed with water forms the crystalline sulphate, $Na_2SO_4 10H_2O$, and in the process absorbs 1.27 times its weight of water. Thus, by adding to the 50 per cent (initial) alcoholic extract enough Na_2SO_4 to remove four-fifths of the water present, the concentration of alcohol is raised to 80 per cent at which protein fractions not containing insulin are precipitated. Much less alcohol has, therefore, to be used and the sodium sulphate can be readily recovered for use again by igniting it.

Besides the mammalian pancreas the principal islets of bony fishes may also be used for preparing insulin. Since the yields from this source, per gram of tissue, are many times greater than from pancreas, the process of manufacture is incomparably simpler and less expensive and the final product is of a high degree of purity. It will be remembered that Diamare (2) originally suggested the anti-diabetic function of these glands (in 1899) and that Rennie and Fraser (12) in 1906 almost succeeded in demonstrating the presence of insulin in them. It was not until 1922, however, that final proof of the presence of insulin in the islets was demonstrated by Macleod, mainly in

the angler or devil fish (Lophius piscatorius) and in the sculpin (Myoxocephalus) and more recently N. A. McCormick and E. C. Noble have found it to be obtainable in very large amount from the islets of the cod (Gadus), pollock (Pollachius) and halibut (Hippoglossus). The islets in these very common fishes being easily recognizable can be removed without difficulty, and since insulin, sufficiently pure for clinical use, can be prepared by extracting them with a relatively small amount of alcohol (enough to give 60 per cent in the mixture which is then removed by vacuum distillation or by warmed air, heating the watery extract to about 80°C. extracting with ether and then applying Dudley's process of purification, this should prove a useful source of supply, at least in maritime countries.

The picrate process has more recently undergone considerable simplification based on the fact that although insoluble in water insulin-picrate is soluble in moist alcohol or acetone, in which protein picrates are insoluble. This makes it unnecessary to apply Collip's alcohol process as the first step in the isolation of insulin picrate. In its simplest form the new process, as used by Dudley on the principal islets of cod fish (Gadus), consists in collecting the material in a saturated solution of picric acid, in which it is transported to the laboratory. The material is then ground in a mortar with the picric acid solution, the residue removed by straining through fine gauze and the residue repeatedly extracted with small amounts of 75 per cent acetone. The acetone is removed from the combined extracts *in vacuo*, and in the watery residue which remains the picrate becomes reprecipitated and this is finally converted into the hydrochloride by the method described above. By this treatment the insulin, by becoming precipitated as the picrate within the material, remains insoluble until the acetone is added and in this state it does not apparently undergo rapid deterioration. We have repeated Dudley's process on cod islets which were collected by a fish buyer and sent to the laboratory by mail at ordinary temperature, with entirely satisfactory results; but on the other hand, we have found that when the much larger islets of the halibut were treated by this method, penetration of the picric acid solution did not occur rapidly enough to prevent rapid deterioration of the material. By attempting this during a three weeks' trip

to the halibut fishing grounds of the Pacific coast most of the material was lost even though considerable picric acid was still undissolved in the preserving fluid. From cod islets Dudley has obtained yields of 40 units per gram of moist tissue. Much larger yields could almost certainly be obtained if strictly fresh material were used but it would probably be advisable to cut up the islets at the time they are placed in the picric acid solution.

Dodds and Dickens have applied a similar method for the isolation of insulin hydrochloride from mammalian pancreas. The fresh gland is repeatedly extracted by aqueous chilled formic acid (to inhibit proteolytic digestion) and this extract then saturated with picric acid. The precipitate is filtered off and the insulin picrate dissolved out by moist acetone. By the addition of water and picric acid solution to this acetone extract the insulin picrate again forms and is collected on a filter and converted into the hydrochloride by Dudley's process.

By the use of methods similar to those employed for preparing insulin Collip, Best and Scott, Winter and Smith, Dodds and Dickens, and Fisher have obtained from various sources such as clams, yeast, onion tops and even, I am told, from grass and potatoes, extracts capable of lowering the blood sugar of normal rabbits. In many cases the action of these extracts is delayed so that it is not until a day, or even longer, after the injection that the blood sugar becomes subnormal. On account of this delayed action Collip has supposed that a substance differing somewhat from insulin is responsible, and this he has called *glukokinin*. Careful examination of Collip's protocols, however, makes it doubtful whether starvation alone may not, in many cases at least, have been responsible for the results and in the last paper published by this worker, this possibility is pointed out. There can be no doubt, however, that insulin-like substances—as judged from the behavior of the blood sugar of normal rabbits—can be prepared from various sources. Sometimes, indeed, as when the salivary glands of normal animals are used, large amounts are found although usually there are only traces. Even the organs and tissues of depancreatized dogs have been shown to contain some insulin (Best and Scott).

These facts may at first sight seem to minimize the significance of

pancreatic insulin as a specific hormone, necessary in the animal body for the prevention of a diabetic state, and the interpretation of the results is difficult. In so far as insulin is obtainable from other tissues than the pancreas of normal higher animals, the explanation is probably that it has been carried into them by the blood, but that insulin should be extractable from those of depancreatized animals, can only mean that it exists as some precursor, for the final conversion of which into insulin in the body, the pancreas, or something derived from it, is necessary, although outside the body this conversion can be partially effected by the chemical reagents which are used as extractives. In any case, this non-pancreatic insulin can be of no use in preventing diabetes in the animal; it must be locked up in the tissues and it can be only when the pancreas is present that an endogenous production—an internal secretion—of sufficient insulin occurs to prevent diabetes. The proof of this assertion is familiar to all in the fact that diabetes of maximal intensity can be induced in animals by one operation only, namely, by pancreatectomy although this diabetes can be entirely prevented by administering insulin. So far as I am aware it has not yet been satisfactorily shown that the same prevention can be effected by using any of the pseudo-insulins. Best and Scott's observations, however, open up a fruitful field for exploration, as also do those of Collip in which it has been shown that injection into a normal rabbit of blood from one suffering from hypoglycemia—induced not only by insulin but in other ways as well—lowers the blood sugar, and that injection of the blood of this second animal similarly affects a third, and so on. Sometimes in these experiments symptoms like those following excess of insulin have been observed, but injections of glucose have not been found to have the usual antidoting influence.

Epstein and Rosenthal have recently reported results which, if they can be confirmed, may serve to throw some light on the nature of glukokinin and the other insulin-like bodies. They state that when a solution of purified trypsin (at a pH of 7) is mixed with insulin (at pH below 4), almost instantaneous inactivation of the hypoglycemic properties of the insulin occurs provided the reaction of the mixture remains on the alkaline side of pH 4.6. This inactivation

occurs as readily at 3°C. as at 37.5°C. and it is accompanied by the formation of an isoelectric precipitate. When the precipitate is removed by centrifuging no effect is obtained with either the supernatant fluid or the precipitate when this is either suspended in water or dissolved in weak alkali. By solution of the precipitate in weak acid (below pH 4), however, all the insulin effects are restored. Even after the insulin and trypsin have been in contact for 42 hours at body temperature, the power of the insulin is not diminished when the precipitate is dissolved in weak acid. It is concluded that trypsin attaches itself to insulin and renders it inert at a pH above 4.6. Inactivation and recovery of insulin can be effected indefinitely by raising or lowering pH, provided the trypsin is active. If it is destroyed either by allowing the reaction to become too alkaline or by heating, its inactivating powers disappear. It would seem that a compound (trypsulin) is formed, which is undissociated under certain conditions. The insulin is not destroyed by trypsin, neither are the proteolytic or milk-curdling effects of the latter disturbed by the combination. The inactivation is not influenced by the presence of serum which however, possesses antitryptic properties when mixed with trypsin alone. When insulin is injected into an animal which has just been injected with trypsin, it is also inactivated. If the insulin is injected first, trypsin may retard its effects.

When larger quantities of purified insulin became available a thorough clinical trial of its therapeutic value was undertaken (cf. Banting and Best, Collip, Campbell and Fletcher (30)), and the results of these will be found on page 68. The present discussion is restricted to the experimental aspects of the work in so far as these bear directly on the clinical use of insulin. These will be considered in two categories: (1) further observations on depancreatized dogs; and (2) observations on normal animals and on other forms of hyperglycemia, particularly with reference to the assay of insulin.

CHAPTER III

Further Observations on Depancreatized Dogs

GLYCOGEN CONTENT OF THE LIVER AND THE HEART

Various workers have confirmed the observation, first made by Minkowski (1), that no glycogen, or only traces, can be found in the liver of depancreatized dogs, even after the animals are fed large quantities of glucose. Minkowski thought, however, that some was deposited with levulose. Cruickshank (31), while confirming these conclusions with regard to glucose, considers that Minkowski's positive results with levulose may have been due to incomplete pancreatectomy, since he himself failed to detect glycogen after feeding with this sugar. We can contribute two observations (32) in which glycogen was determined in depancreatized dogs that were given large quantities of sugar for some time before death. In one of the animals, which lived for seven days following pancreatectomy, cane sugar was fed in large amounts during the last three days of life and 1.32 per cent of glycogen was found in the liver; in another, which lived for eleven days and received sugar for several days before death, only 0.046 per cent was found. In neither of these animals did the cane sugar cause any change in R.Q. Since serial microscopic sections of the duodenum were not made, it is possible that a trace of pancreatic tissue may account for the glycogen formation in the one animal.

In any case we can be certain that even by feeding with cane sugar very little glycogen becomes deposited in the liver of depancreatized dogs, which contrasts very strikingly with the result which is obtained when insulin is given at the same time as the sugar. The first observation in which this was done was made on a dog (15 kgm. weight) that had been depancreatized during nine days (December 14 to 22, 1921), no insulin being given until two days before death. Although only the crude extract was available for administration, it lowered the

blood sugar from 0.309 per cent to 0.051 per cent, in spite of the fact that, at the same time, large amounts of cane sugar were fed to the animal, which it took greedily. Analysis of the liver by Pflüger's process was found (by J. B. C.) to contain an unprecedented amount of glycogen (over 20 per cent). Other observations of a similar nature are shown in table 1 (32). For comparison, results obtained on depancreatized dogs to which insulin was not given are shown in table 2

TABLE 1

DATE	DAYS DEPANCREATIZED	DAYS DURING WHICH INSULIN AND SUGAR WERE GIVEN	PER CENT GLYCOGEN IN LIVER
February 21 (1922)	7	5 days	12.58
January 14	4	Less than 1 day	2.70
April 28	3	2 days	11.40
May 2	5	1 day	4.80

TABLE 2

DATE	DAYS DEPANCREATIZED	GLYCOGEN CONTENT	
		Liver	Heart
		per cent	*per cent*
April 24 (1923)	5	0.09	0.47
May 1*	4	Trace	0.38
May 4	5	Trace	0.12
May 5	3	0.06	0.61
May 7	4	0.06	0.33
May 11	3	0.07	0.65
May 14	4	0.03	0.66

(McCormick (33)). In these, except the one asterisked, the animals were under ether anesthesia for at least one hour before being killed.

In several of the observations glycogen was also determined in the muscles and the heart. Nothing conclusive can be made out from the analyses on the skeletal muscles but there is evidence that insulin causes reduction in the amount of glycogen in the heart in which, as histological examination by previous workers had shown, unusually large deposits of this substance occur, both in diabetic patients and in depancreatized dogs. Cruickshank (31) found by analysis (on 16 depancreatized dogs) the average percentage of glycogen to be 0.7

compared with 0.5 per cent in normal animals (6 observations). We found 0.79 to 0.92 in different portions of the heart of one depancreatized animal fed sugar but not given insulin, and 0.98 per cent in that of another similar animal. In 4 depancreatized animals to which insulin, as well as sugar, was given the values were 0.725, 0.600, 0.570 and 0.296 per cent respectively. It must be pointed out, however, that although the glycogen content of the heart is often high in depancreatized dogs this is not invariably so. Out of the 7 animals reported above, it will be seen that high percentages occurred in only 3, and that it was very low in 1 case (0.12 per cent). The ether anesthesia may account for the unexpectedly low percentages of glycogen found in this series of observations.

FATTY ACID CONTENT OF THE LIVER AND BLOOD

It is well known that in diabetes the percentage of fats rises both in the liver and the blood. In the former, as the glycogen disappears fats accumulate and may reach a very high percentage (over 20 per cent); in the latter, especially in the terminal stages of the disease, percentages of over one are not uncommon. The effect of insulin on the total fatty acids, determined by Leathes' modification of the Kumagawa-Sato method, is shown in table 3.

In two of the observations, Nos. 53 and 54, the results are not conclusive since such excessive doses of insulin were administered that death from hypoglycemia occurred within twelve to eighteen hours. There is sufficient evidence from the other results, however, to show that insulin reduces the fat content of both liver and blood. The effect of insulin on the blood fat appears to be developed within a few hours which is of interest on account of the similar prompt effects of this hormone on the excretion of the ketone bodies. As far as can be judged from the available analyses the effect on the liver fat is not so prompt, which indicates, when taken in conjunction with the behavior of the blood fat, that the removal of fat from the liver must proceed at a pace which is conditioned upon the rate at which it can be deposited in the fat depôts or converted into other lipoid substances. The remarkable effect of insulin on lipemia in diabetes mellitus has been repeatedly confirmed in the clinic.

EXCRETION OF KETONE BODIES IN THE URINE

The oxidation of fats in the animal is believed to take place at the β-carbon atom (i.e., the C atom two places removed from the COOH group) the process of proceeding smoothly, step by step, until all the

TABLE 3

Total fatty acids in depancreatized dogs, with or without insulin

NUMBER OF ANIMAL OR DATE OF OBSERVATION	TOTAL FATTY ACIDS		REMARKS
	Liver*	Blood†	
48	12.25		
50	14.10	1.21	Fed sugar but insulin not given
51	9.90	1.12	
52	7.428	0.30	Sugar + insulin 1 day
55	2.190	0.53	Sugar + insulin 2 days
56	4.41		Sugar + insulin 1 day
53	10.28		Sugar + overdose insulin‡
54	26.36	0.37	Sugar + overdose insulin‡
April 24	25.3 23.9	1.07 1.08	
April 27	12.80	1.02	
May 1	12.75	1.13	Not fed sugar nor given insulin
May 4	33	1.58	
May 5	8.8	0.72	The number of days since pancreatectomy
May 7	23.1	0.74	will be seen by comparing dates given in
May 11	15.6	0.85 0.91	previous table
May 14	26.24	0.76 0.79	

* Leathes' method.

† Bloor's method.

‡ These animals died within a few hours after insulin.

methyl radicles have been consumed. In diabetes it is believed that this process is carried only so far, leaving a residue still containing three methyl radicles, one of which, in the β-position, undergoes partial oxidation forming a series of substances known as the ketone bodies β-oxybutyric acid, aceto-acetic acid and acetone ($CH_3CHOH \cdot CH_2 \cdot COOH$; $CH_3 \cdot CO \cdot CH_2 \cdot COOH$; $CH_3 \cdot CO \cdot CH_3$). Probably, however,

the order is reversed, aceto-acetic acid appearing first, β-oxybutyric acid and acetone resulting from it by reduction and oxidation respectively. According to another school (consult Geelmuyden) the ketone bodies have a greater significance than this and represent intermediary bodies in the conversion of fat into carbohydrates. In any case, whether incompletely oxidized residues in the combustion of fat, or stages in the conversion of fat into carbohydrate, the ketone bodies accumulate in the blood and tissues and appear in the urine whenever there comes to be a deficiency in carbohydrate metabolism,

TABLE 4

Excretion of sugar and ketone bodies in depancreatized dogs

NUMBER	DATE	INSULIN GIVEN	TOTAL URINE	TOTAL DEXTROSE EXCRETION	TOTAL ACETONE BODIES	REMARKS
			cc.	*grams*	*mgm.*	
11	January 6	No	1,000	29.7	100	
	January 7, a.m.	No	375	28.4	187	Blood sugar 0.351 per cent
	January 7, p.m.	Yes				Blood sugar 0.085 per cent
	January 8	No	425	4.25	None	
	January 9	No	325	9.95	None	
	January 10	No	370	9.6	None	
	January 11	No	275	25.2	34	
	January 12	No	325	25.4	55	
	January 13, a.m.	No	750	18.0	114	
	January 13, p.m.	Yes				
	January 14	Yes	600	8.0	None	

such as occurs in diabetes; and serious poisonous effects are produced (coma), due partly to their acidic properties. Insulin promptly reduces the ketone-body excretion in the urine of depancreatized dogs. Thus, in one of the earlier observations the daily excretion of ketone bodies steadily rose during the seven days following pancreatectomy, from 75 to 210 mgm., the daily sugar excretion meanwhile varying between 24 and 36 grams. On the seventh and eighth days massive doses of (crude) insulin were given along with sugar, and both the ketone bodies and the sugar disappeared entirely from the urine. (This is the same animal on which the first glycogen determination was made, see page 20.)

In another animal the results given in table 4 were obtained.

More recently, in collaboration with Chaikoff and Markowitz, the exact time relationships of the changes caused by insulin on the sugar, the ketone bodies, the phosphoric acid and fat of the blood have been determined on diabetic dogs. It has been found in observations made at half hour intervals that the sugar, ketone bodies and phosphoric acid all come down at the same time and fall at strictly parallel rates. During recovery, however, the phosphoric acid rises before the blood sugar or ketone bodies. The fat does not fall at the same time as the others. It is also of interest to note here that the sugar and the ketone bodies were both much higher in a fat, depancreatized dog than in a thin one.

BEHAVIOR OF THE RESPIRATORY QUOTIENT

It is generally recognized that the most satisfactory evidence of the utilization of carbohydrate in the animal body is afforded by the behavior of the respiratory quotient, i.e., the ratio between the volumes of CO_2 expired and O_2 absorbed. In the normal animal this quotient approaches unity in proportion as carbohydrates replace fats and proteins in the total metabolism; thus, when sugar is given to animals that are starving or living on a fat and protein diet the quotient rises. In the completely diabetic animal, on the other hand, whether this condition be brought about by removal of the pancreas, by administration of phloridizin or by disease, the quotient remains at the level of about 0.7 or below it (which is characteristic of the metabolism of a mixture of fat and protein) even when large amounts of carbohydrate are ingested. Under these conditions the quotient may actually fall somewhat.

To test the effect of insulin in diabetes, the expired air of depancreatized dogs was collected in a Tissot spirometer and analyzed by the usual technique (by Hepburn and Best (35)). The procedure followed was to determine R.Q. for periods preceding and following the administration, by mouth or subcutaneously, of cane sugar or glucose, and then to repeat the observation giving insulin along with, or prior to, the sugar. Since previous investigators (Murlin (15)), Verzar (36), etc.) had shown that the power to oxidize carbohydrate,

as revealed by the behavior of R.Q., does not entirely disappear until about four days following pancreatectomy the observations were not made until after this period. The following is a typical result:

DATE	CONDITION	R.Q.
1922		
January 20	Normal dog, starved 24 hours	0.85–0.86
	35 minutes after 30 grams sucrose	1.0
	1 hour 25 minutes later	1.0
January 21	Pancreas removed	
January 23	No sugar or insulin	0.63
	1½ hours after 20 grams sucrose	0.77
January 24	30 minutes after 25 grams sucrose and insulin	0.86
	1½ hours later	0.90
	3 to 3½ hours later	0.77
January 25	No sugar or insulin	0.68
	various periods after 20 grams sucrose	0.82, 0.82, 0.85
January 26	No sugar or insulin	0.68–0.72
	1 hour after 20 grams sucrose	0.81
	5 hours later and 40 minutes after insulin	0.90

In another animal, six days after pancreatectomy, sugar and insulin raised the quotient to 0.95 whereas in previous observations with sucrose alone it rose only from 0.63 to 0.70. The results show that in depancreatized animals insulin and sucrose cause a greater rise in R.Q. than occurs with the same quantity of sucrose alone. In both the earlier and the more recent observations the effect of insulin in raising the respiratory quotient in depancreatized dogs has been observed to persist with gradually lessening potency, for about two days following the injection. These results indicate that the action of insulin on diabetic dogs can be detected for a longer time, following the injection, when the behavior of the respiratory quotient is used to indicate it, than when the level of the fasting blood sugar is used (cf. fig. 1).

Similar results have been obtained by S. U. Page (36c) in phloridzin

diabetes. Thus, in a dog which was injected daily with 2 grams of this drug and was on a constant meat diet, the R.Q. remained at about 0.7 and was unaffected by giving 40 grams of sucrose subcutaneously. When insulin was given as well as sugar, however, R.Q. rose, as shown in table 5.

In the observations made during July the daily diet was 400 grams meat and in those made during September it was 600 grams. The excretion of glucose in the urine collected during twenty-four hour periods was also measured but the results did not demonstrate a marked decrease as a result of insulin. The excretion of ketone bodies was diminished by the injections. More recently M. Ringer (36a) and Nash (36b) have made similar observations under more carefully controlled conditions. Ringer found that when 40 grams glucose were given along with insulin (20 units) 12.2 grams failed to reappear in the urine and R.Q. rose from 0.71 to 0.75 indicating that about 6 grams could be accounted for by increased oxidation. On another occasion R.Q. rose to 0.84. The experiments on the combined effects of insulin and phloridzin are difficult to conduct because hypoglycemic symptoms are very readily induced. It is on this account that Page was unable to obtain satisfactory results on the influence of insulin on the excretion of sugar in the urine. Ringer suggests that the effect of insulin on phloridzin diabetes might be used as a basis for its assay. We do not believe that the method is likely to prove one of practical value.

Reviewing these results as a whole it is clear that insulin plays an essential rôle in the metabolism of carbohydrates, as well as of fats. Both types of metabolism proceed in the normal animal through an extended series of chemical changes. In the case of carbohydrates, glucose, after its absorption, becomes either polymerized to glycogen and stored in this form, or gradually broken down into simpler products which are finally oxidized. It is possible that glycogen formation is a necessary preliminary step to this catabolism. What the intermediary products may be is unknown, but there are reasons for believing that they are numerous and that they exist in a certain balance with one another. In such a case it is evident that the failure of *one step* in the break-down process would interfere with the entire process.

It has been suggested by Winter and Smith (37) that the first step

is the conversion of glucose into a more reactive form and that insulin is necessary for its occurrence. Chemically considered ordinary glu-

TABLE 5

Effect of insulin on R.Q. in phloridzin diabetes

DATE	TIME	CONDITION	R.Q.
1922			
July 5		Phloridzin, 2 grams daily, started.	
July 10	10:30 a.m.		0.70
	12:00 n.	40 grams sucrose	
	1:15 p.m.		0.71
July 11	10:15 a.m.		0.67
	11:50 a.m.	Insulin	
	12:50 p.m.	40 grams sucrose	
	2:15 p.m.		0.91
July 12	10:30 a.m.		0.72
	1:00 p.m.	40 grams sucrose	
	2:15 p.m.		0.83
September 2		Phloridzin, 2 grams daily, started.	
September 8	10:10 a.m.		0.71
	12:10 p.m.	40 grams sucrose	
	1:25 p.m.		0.76
September 9	9:25 a.m.		0.72
	10:50 a.m.	Insulin	
	11:00 a.m.		0.70
	1:15 p.m.		0.92
September 11	10:15 a.m.		0.79
	1:15 p.m.	40 grams sucrose	
	2:30 p.m.		0.84
September 13	9:30 a.m.		0.74
	10:50 a.m.	Insulin	
	12:55 p.m.	40 grams sucrose	
	1:10 p.m.		0.88

cose is an equilibrated mixture of two varieties, designated α and β, and characterized by differences in their power to rotate the plane of

polarized light. In both of these the carbon atoms are joined in a ring formation which makes them relatively stable. In the more reactive form, designated γ-glucose, the rotary power is different (rotates to the left instead of to the right) and it is believed that the molecule has become less stable because of a shifting in the position of the ring (Irvine (38), etc.). These varieties cannot be identified by reduction tests alone, but only by comparison of their reducing and rotatory powers. Using this method, Winter and Smith have claimed that γ-glucose can be detected in normal blood (of laboratory animals and men) but not in diabetic blood, in which, however, it appears when insulin is given. Too much weight must not be placed on these results, however, partly because the differences (in rotatory power) observed were very small, partly because very complicated processes had to be employed to remove the proteins from the blood and partly because the results have not so far been confirmed by other workers. Using the same technique G. S. Eadie (39) has indeed obtained polarimetric readings similar to some of those reported by Winter and Smith for normal blood, but on the contrary he has also obtained others of an exactly opposite character. Winter and Smith publish very few protocols so that it is difficult to appraise their work correctly. One serious objection to their conclusions is that they do not adequately rule out other possible explanations for their results. Prior to the work of Winter and Smith, Hewitt and Pryde (40) had stated that optical evidence of the formation of γ-glucose can be obtained when a solution of glucose is placed on a loop of the intestine for a short time. Stiven and Waymouth Reid (41) and more recently van Creveld (42) have shown, however, that such is not the case and the last mentioned worker has also been unable to confirm any of Winter and Smith's conclusions.

Apart from this no attempt has so far been made to determine the exact stage in carbohydrate metabolism for the consummation of which insulin is required. That both the formation of glycogen and the oxidation of glucose are interfered with in diabetes indicates that a relationship must exist between the two processes and this can be explained most simply by supposing that glucose, before it proceeds to final oxidation, must pass through a glycogen stage for which insulin

is necessary. There is no direct evidence at present to support this view but it is at least significant that after pancreatectomy, the respiratory quotient does not reach its final low level, of about 0.65, until all the glycogen has disappeared from the liver. It remains to be determined whether some glycogen is formed prior to the increase in respiratory quotient, when sugar and insulin are given to diabetic animals. Such an hypothesis would place glycogen in a more important position in metabolism than that of a mere storage form of carbohydrate. Formation of glycogen may be a necessary step in the metabolism of sugar and it is conceivable that it is so because the glucose which is formed by its hydrolysis in the body is of a different type from the α-β-glucose from which it was built up. An important objection to this hypothesis is that glycogen is a polymerized form of glucose and therefore a step further away than glucose itself from the break-down products which finally become oxidized. It is easier to imagine that insulin, perhaps in association with a co-enzyme, converts glucose into some active form which is then used to meet the demands of the tissues for carbohydrate, and that the remainder is polymerized into glycogen and stored until no more is being absorbed from the intestine, when the glycogen again breaks down to glucose. The persistence of glycogen in muscle and particularly in the heart after the liver has become glycogen-free, as in diabetes and acute starvation, would, however, seem to indicate that it must be more than a mere storage material. Under these conditions it is formed at the expense of protein, and, it is pertinent to enquire why should it be so unless it is an essential step on the road to oxidation?

Turning now to fats, it is again significant that in diabetes the long series of changes through which they pass should be interfered with at both ends of the metabolic chain, as it were, and that insulin should not only restore to normal the migration of fat between the liver and tissues but also rectify the faulty oxidation. It is usually stated that fats burn in the fire of carbohydrates, but the exact relationship between the metabolism of these two substances is not clearly understood. Although much progress has recently been made towards furnishing an answer to this problem, it cannot be said that enough is known to make it possible to understand how insulin brings about these effects.

As already remarked, some writers, such as Geelmuyden, believe that the ketone bodies are really intermediary substances between fat and carbohydrate and that they accumulate in the body in diabetes because this transformation has been interfered with. According to this view we may imagine that the function of insulin is to regulate—retard—the transformation so that when this hormone is absent, as in diabetes, fat changes into sugar in such excessive quantities that it cannot be oxidized with the result that sugar, as well as the ketone bodies, accumulates in the organism, and excessive quantities of fat appear in the blood and liver. The low R.Q., according to this view, would be explained by the constant necessity for oxygen to convert fat into carbohydrate and the failure of the quotient to rise when sugar is given, to the fact that ultimate oxidation of sugar, being already at its maximum, cannot be further stimulated. The only real difficulty in accepting this interpretation is in connection with the behaviour of glycogen, but it is equally difficult to explain this according to the usual theory of diabetes, according to which the diabetic state is primarily dependent upon faulty oxidation of carbohydrate in the tissues.

GLUCOSE EQUIVALENT OF INSULIN

The glucose equivalent of insulin means the number of grams of glucose which a given quantity of insulin can cause to be metabolized in a diabetic animal (depancreatized dog), and it is measured by comparing the glucose balance of one period during which a certain amount of insulin is given with that of another period during which the amount of insulin is changed (43). A method based on this principle has been used in the clinic but the results have been inconstant, due in part, no doubt, to the fact that the diabetic patient retains some remnant of islet tissue still capable of yielding an endogenous supply of insulin which is not constant from day to day.

The animals after pancreatectomy were fed daily with a liberal quantity of flesh (500 to 600 grams) as free from fat as possible, and 100 to 150 grams of cane sugar. This ration was given twice daily and insulin injected subcutaneously immediately before each feeding. The total daily glucose excretion was compared with the glucose intake

(i.e., cane sugar × 1.053 *plus* glucose from protein obtained by multiplying urinary nitrogen by 3.625). The difference between excretion and intake gives the amount of glucose metabolized in twenty-four hours. When this is determined for two periods during which different amounts of insulin are given it is easy to compare the glucose equivalents of the insulin. The following facts have been established: (1) The glucose equivalent of the same dose of insulin given on different days of equal glucose intake varies within a relatively narrow range. (2) It is relatively much larger (per unit of insulin) with small than with large doses of insulin. (3) It becomes greater (per unit) when the amount of ingested carbohydrate is increased. The first two conclusions are based on the following results (F. N. Allan):

Dog 1. Fed 600 grams meat and 100 grams sucrose.

INSULIN GIVEN PER DAY (CLINICAL UNITS)	GLUCOSE EQUIVALENTS ON DIFFERENT DAYS
20	5.8, 5.8
24	4.1, 4.0
32	3.5, 3.5, 3.6, 3.3, 3.7, 4.1
36	3.0, 3.1, 3.1
38	3.4
40	3.0, 3.3, 3.1, 3.0

The third conclusion is based on the following:

Insulin given daily 20 units

SUGAR GIVEN PER DAY	GLUCOSE EQUIVALENTS ON DIFFERENT DAYS
gms.	
50	3.5, 3.9
100	5.8, 5.8
150	8.4, 8.1, 6.9, 6.9

The interpretation of these results is that when the amount of insulin exceeds a certain optimum some of it does not have an opportunity of affecting the metabolism of glucose. This may, in part, be due to the fact that with larger amounts of insulin some is excreted before it can act on the sugar, but other factors must also come into play as is clear from the results obtained by keeping the insulin dosage constant but varying the sugar intake (third conclusion). The action of insu-

lin on glucose metabolism no doubt proceeds according to the same general laws as govern enzyme action, namely, that the amount of substrate which is acted on is not a linear function of the amount of enzyme but is relatively much greater when there is a large excess of substrate compared with the amount of enzyme. This latter condition is fulfilled when small amounts of insulin are given, or when, with larger amounts, the intake of sugar is increased. The same relationships between dosage and effect are seen in the pressor action of epinephrin and no doubt apply for drugs in general (cf. Murray Lyon (44)).

There are two practical applications of these results. One of them is of clinical importance, for it indicates that even very minute doses of insulin may be of great advantage to the diabetic patient in enabling him to metabolize much more glucose than he otherwise could. Suppose, for example, that we give one unit of a certain preparation of insulin to a patient who is excreting a large amount of sugar, it will cause many more grams of sugar to disappear from the daily urine than if we give the same amount to a patient that is almost sugar-free. The other is pharmacological, since it indicates a possible method for the accurate assay of insulin. Instead of expressing the dosage in terms of the power to lower the blood sugar of normal rabbits, upon which the present unit is based, it may be done in terms of glucose equivalents. But it is clear that we cannot state that one unit of insulin will cause so many grams of glucose to be metabolized, unless we know the glucose balance at the time the insulin is given.

Allan has more recently thoroughly tested the possible value of this method for assay purposes of insulin but has not found that it offers any advantages over the rabbit method described elsewhere (59).

The relation between insulin and glucose equivalents is such that when the logarithms of the amount of insulin given (expressed in rabbit units) are plotted against the logarithms of the glucose equivalents (the intake of glucose being constant), the points fall along a straight line, represented by the equation $\log g = 1.86 - 0.85 \log u$ and which may be expressed in the form $g\ (u)^{0.85} = 10^{1.86}$. The curve corresponding to this equation is given in figure 2 in which, also, the glucose equivalents (ordinates) actually found in two different

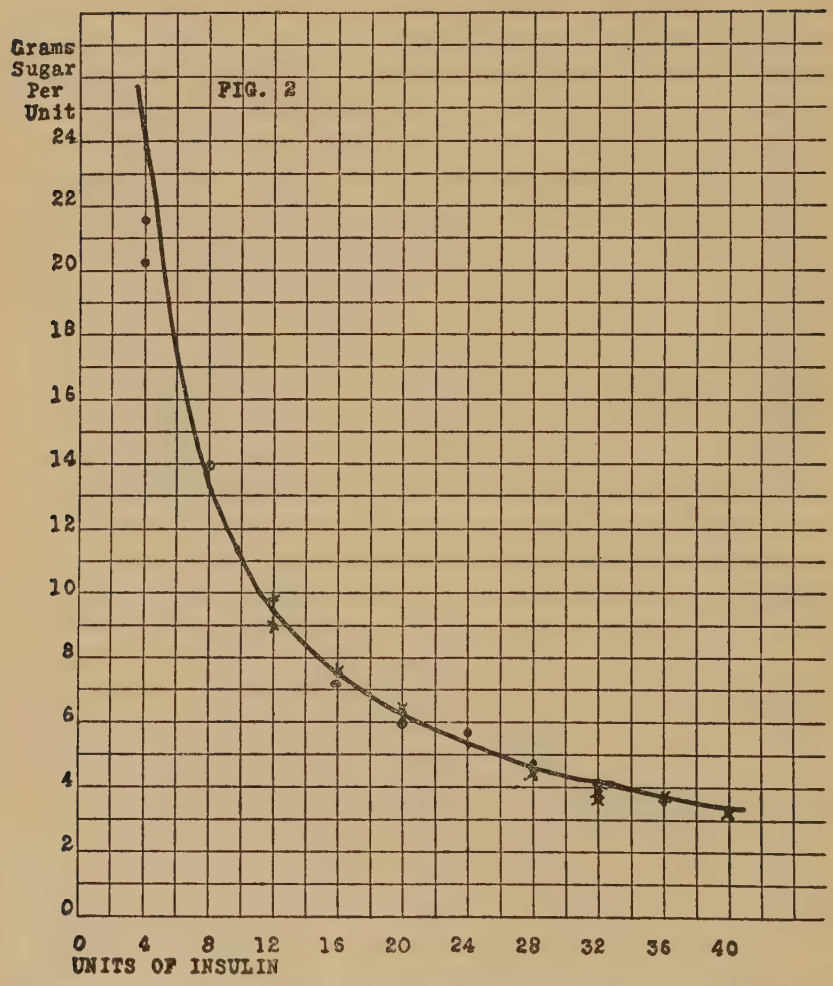


FIG. 2. CURVE TO SHOW RELATIONSHIP BETWEEN GLUCOSE EQUIVALENTS AND VARYING DOSES OF INSULIN

The curve corresponds to the equation $g\ (u)^{0.85} = 101.86$ and the dots and crosses give the results obtained in observations on the different animals. The upper part of this curve should probably bend towards the left and pass somewhere between the two dots on the 4 unit line. One unit of insulin, given alone, would therefore account for about 23 grams of glucose.

animals for different doses of insulin (abscissae) are indicated by dots and crosses. Failure to recognize the fact that the glucose equivalent of each unit of insulin is greater with small doses than with large, explains in part at least the considerable variations obtained by clinical investigators. Taking the most dependable of those published by Wilder, Boothby (45), etc. the equivalent per unit was found to run between 0.9 and 3.1 grams with an average of 1.45 grams. Woodyatt (46) gives the average at 1 to 1.6 grams. These values for the human diabetic are considerably lower than those found for depancreatized dogs fed on sugar. Is it possible that they might be less in the latter, if the animals were fed exclusively on a meat diet?[1]

This raises the question as to whether the glucose derived from protein is metabolized with equal facility to that derived from carbohydrate sources. Wilder, Boothby, Barborka, Kitchen and Adams (45) have noted that the same dose of insulin, given to a diabetic patient at one period when the diet contained a high proportion of protein, caused much less reduction in the glycosuria than it did at another, when the protein was largely replaced by carbohydrate, the caloric and total glucose values of the two diets being kept the same. Thus, while on a diet made up of 45 grams protein, 142 grams fat and 11 grams carbohydrate (i.e., 150 grams available glucose and 1956 cal.) 15 units of insulin reduced the daily sugar excretion from 57.78 to 9.46, giving a glucose equivalent of 3.32, whereas while on a diet of 159 grams protein, 118 grams fat and 41 grams carbohydrate (i.e., 145 grams available glucose and 1907 calories) 15 units only reduced it from 76.10 to 47.15, giving a glucose equivalent of 1.9. This would seem to indicate that the sugar derived in the body from protein is not so readily metabolized under the influence of insulin as sugar that is absorbed as such from the intestine.

[1] Further discussion of the glucose equivalents of insulin on diabetic patients will be found in the clinical part of this review (page 79).

CHAPTER IV

Effect of Insulin on Normal and Hyperglycemic Animals

effect of insulin on normal animals

It would serve no useful purpose here to enter into details with regard to the effects of insulin on normal and hyperglycemic animals, but a brief outline of the main results is necessary to an understanding of the highly practical question of its physiological assay. A full discussion of this subject will be found elsewhere (47).

Within a few minutes of the intravenous or subcutaneous injection of insulin into rabbits, the percentage of blood sugar begins to fall and it continues to do so at a practically uniform velocity for about forty to sixty minutes. This "initial fall" is not noticeably influenced by the nutritional state of the animal until a certain low level is reached (about 0.045 per cent) when the curve either begins to rise again as in well-fed animals, or continues to fall, usually at a decreasing velocity, as in animals that have been starved. The extent to which the blood sugar ultimately declines in starved animals depends partly on the dose of insulin, and under certain conditions the sugar may reach the vanishing point. These differences in the behavior of the curve are primarily dependent upon the amount of glycogen stored in the body, particularly in the liver, the recovery being dependent on the fact that when the blood sugar has declined to a certain level, the glycogenolytic function of this organ becomes stimulated, so that more glucose is discharged into the systemic blood. This stimulation occurs through the nervous system, since Burn (48) has found that when ergotamine is given along with insulin to well-fed animals the blood sugar curve fails to recover and behaves like that of a starved animal, an observation which has been confirmed by McCormick. This alkaloid acts like ergotoxine in paralyzing the endings of the sympathetic (thoracic-autonomic) nerve supply. We must suppose, therefore, that the so-called glycogenic center becomes stimulated when the blood sugar reaches a certain low level.

As to the cause for the initial fall in blood sugar, little is known for certain at present. Insulin does not have any influence on the rate at which sugar disappears from blood after its removal from the body (glycolysis) either when the insulin is added to the blood directly or when it is injected into the animal prior to bleeding (Eadie and Macleod (49)). We must conclude that the sugar disappears from the blood because of more rapid diffusion into the tissues, consequent upon a lowering of its intracellular tension. In other words, insulin must cause a sort of vacuum for sugar to be set up in the tissues, to fill which sugar is removed first of all from the blood and later, through the blood, from the glycogen stores of the liver. Further evidence that insulin accelerates the rate at which sugar passes into the tissues is afforded by the fact that its addition to Locke's solution perfused through the excised mammalian heart markedly increases the rate at which glucose disappears from the solution (Hepburn and Latchford (50) and Burn and Dale (48a)).

The question therefore, is: What causes the vacuum for sugar in the tissues? Since, as we have seen, insulin leads both to increased formation of glycogen and to increased oxidation of glucose when it is given to diabetic animals, it might be assumed that the same two processes must be responsible for its disappearance in normal animals. With regard to glycogen formation, however, the evidence is very clear that insulin, instead of stimulating the process, has the opposite effect. Less glycogen is deposited, both in the muscles and the liver, when insulin is given along with sugar to previously starved animals than when the same amounts of sugar are given alone (McCormick and Macleod (51)) and the glycogen particularly in the muscles becomes markedly reduced in amount when insulin is given to previously well-fed animals (Dudley and Marrian (52)). Regarding the possibility that carbohydrate combustion is stimulated by insulin the evidence is not so clear, since observations on the respiratory exchange in different types of animal do not give entirely similar results. In dogs insulin causes a slight increase in R.Q. occurring as a rule during the first hour or so following its injection (i.e., during the time the blood sugar curve is falling rapidly) but this is followed later by a return to the original level. A rise occurs in the intake of oxygen,

starting as a rule in about two hours after the injection of insulin, and the extent of this rise is more or less proportional to the dose. The volume of air breathed, the rate of breathing and the pulse rate all increase parallel with that of oxygen consumption and it can be noted that hyperexcitability of the animal and increased muscular tone, accompanied often with perceptible twitching, become evident at the same time and run parallel with the respiratory changes. These symptoms, as we shall see later, are related to the hypoglycemia and can be antidoted by giving glucose. When this is done the intake of oxygen does not become increased. In one dog, and to a less extent in another one, Pember and Dickson several times observed that R.Q. rose to over unity (1.2 to 1.3) following insulin, but as a rule, as already stated, this did not occur and at present we cannot account for the irregularity in the results, although there is reason to believe that it is related to the nutritional condition of the animal. In rabbits, following insulin, R.Q. also becomes increased and the intake of oxygen may either rise, or remain practically constant, or decline somewhat depending upon whether or not the hypoglycemic symptoms become prominent (53). In curarized rabbits, in which no muscular hypertonicity can develop, the O_2-intake, according to Krogh (54) usually declines slightly. In mice there is a marked decline in the intake of oxygen (Dudley, Laidlaw, Treven and Boock (55)) and CO_2, so that while R.Q. may rise this cannot indicate increased combustion of carbohydrate. In man, Kellaway and Hughes (56) and also Lyman, Nicholls and McCann (57) found that when insulin is given in sufficient dosage to induce the earliest symptoms of hypoglycemia, R.Q. becomes raised. According to Kellaway and Hughes the oxygen intake does not increase sufficiently so that the sugar which has disappeared from the blood can be entirely accounted for by increased combustion of carbohydrate.

Taking these results as a whole the following conclusions concerning the mechanism of the action of insulin on normal animals seem warranted: (1) the amount of free glucose in the tissues (tension of glucose) promptly becomes reduced so that sugar is removed from the blood; (2) this reduction is not dependent upon a polymerization of glucose into glycogen; (3) it is not entirely due to an increase in the

relative amount of carbohydrate undergoing combustion, although this may occur to some extent under certain conditions.

It would appear, therefore, that insulin causes the glucose to be converted into some substance which is not precipitated as glycogen although it has lost its reducing properties. The identity of this substance is as yet unknown but since it has been found that the inorganic phosphates of the blood become reduced at the same time as the reduction in blood sugar, it is possible that it may be related to hexose phosphate. Certain observers have stated that an increase occurs in the so-called lactacidogen phosphorus of the muscles of animals injected with insulin frozen immediately after death by means of liquid air, the technique employed being that of Embden. Using cold alcoholic (70 per cent) extracts of muscles we have not been able to find any increase in lactacidogen phosphorus as a result of injections of insulin and sugar into rabbits. It has also been suggested that the high respiratory quotients sometimes observed after insulin indicate that fat-like substances are produced (cf. Macleod: Proceedings of the Institute of Medicine of Chicago, February, 1923). In this connection it should be noted that Dudley and Marrian did not find the amount of fatty acid in the liver to be changed in normal mice following insulin and Dudley has found that there is a decrease in total lactic acid in the muscles. Lactic acid is not significantly increased in the blood.

Hypoglycemic symptoms

When the blood sugar reaches a level of about 0.045 per cent, in rabbits, peculiar symptoms supervene. Preceded usually by a period of hyperexcitability, these then take the form of violent convulsive seizures, not unlike those of acute asphyxia, and between the seizures the animal may either remain in a hyperexcitable condition or gradually pass into one of coma which becomes more and more pronounced until death of the animal. In small animals, such as mice, coma and paralysis are the prominent symptoms.[1]

These symptoms are immediately removed by restoring the lost glucose to the blood. This may be done either by injecting glucose

[1] The symptoms in man are described elsewhere (page 97).

subcutaneously, or intravenously, or by oral administration of any sugar which will yield glucose during its digestion. The latter method can of course only be adopted when the animal is still conscious and can swallow. Injection of epinephrin or pituitrin also removes the symptoms, the mechanism in the case of the former being that glycogenolysis is stimulated in the liver, thus adding glucose, endogenously, to the blood. This method should only be used on diabetic patients when it is certain that there is glycogen stored in the liver. Glucose is remarkably specific in its antidoting action. Of the other monosaccharides mannose and levulose are also effective and, to a less extent, galactose. The only disaccharide having any beneficial action is maltose, but this is somewhat delayed (Noble and Macleod).

More recently these observations have been extended in collaboration with P. T. Herring and J. C. Irvine, in order to determine to what extent the glucose molecule could be altered without affecting its power to antidote the symptoms. By employing the various methyl derivatives of glucose it has been found that even the slightest change such, for example, as substitution of one hydroxyl group entirely destroys the antidoting properties.

EFFECT OF INSULIN IN EXPERIMENTAL HYPERGLYCEMIA

As is well known there are in general two methods by which, apart from pancreatectomy, the percentage of sugar in the blood may be caused to increase. These may be classified as *exogenous* and *endogenous*. Exogenous hyperglycemia is brought about by injection of glucose subcutaneously or intravenously, or by feeding with any carbohydrate which is converted into glucose during the digestive process, and endogenous, by the various experimental procedures which are known to stimulate increased hepatic glycogenolysis. These procedures may be further divided into three groups, nervous, asphyxial and toxic. Among the nervous forms are puncture of the medulla oblongata, stimulation of the sympathetic nerve supply of the liver and the injection of epinephrin. The asphyxial hyperglycemias include those due to mechanical asphyxia, to poisoning by carbon monoxide and, to a certain extent, to the action of anesthetics. As examples of the toxic forms may be mentioned morphine and the anesthetics.

It is significant that insulin in suitable dosage is capable of preventing the development of hyperglycemia in all of these conditions (58). This fact is of importance in relation to the problem of the assay of insulin, which will be discussed immediately, and it is also of interest from the physiological standpoint. In the latter connection let us briefly consider the antagonistic action of epinephrin and insulin. There are two mechanisms by which insulin might prevent the development of epinephrin hyperglycemia, these are: (1) by suppressing the hyperglycogenolysis; (2) by removing from the blood the extra sugar resulting from this process, as quickly as it is formed. In collaboration with E. C. Noble and M. K. O'Brien we have found, by measurement of the amount of glycogen in the liver in well-fed rabbits, that more of this substance disappears in a given time with epinephrin alone than with (the same amount of) epinephrin *plus* insulin, indicating clearly that insulin inhibits the hyperglycogenolytic effect of epinephrin. This result is of especial significance since, as we have seen, insulin given alone to well-fed animals itself causes hyperglycogenolysis. At the same time as it diminishes hyperglycogenolysis, however, insulin also accelerates the rate at which the sugar is removed from the blood, as is clearly shown by its effect on the exogenous form of hyperglycemia (page 57). These observations are quoted here to indicate the futility of attempting to explain the mechanism of the action of insulin until much more is known of its effects, both on normal and diabetic animals. There are already in the literature so many different views with regard to this question that it would occupy several pages to expound them and at the end we should be no nearer the truth.

CHAPTER V

Effect of Insulin on the Metabolism of Phosphorus

That a close relationship exists in the animal body between the metabolism of sugar and that of phosphorus has been demonstrated in a variety of ways. Thus, Fiske observed that the ingestion of sugar caused an immediate decrease in the excretion of phosphorus, followed by an increase to above the normal level, and Blatherwick, Bell and Hill found under similar conditions that the blood phosphates undergo reduction. In the hyperglycemia produced by epinephrin changes in the phosphates of the blood and urine have also been recorded by Perlyzweig, Latham and Keefer and by Winter and Smith. Of further interest in this connection is the fact discovered by Elias and Weiss that the blood sugar becomes reduced in amount when solutions of phosphates are injected intravenously into animals in which the blood sugar has been raised above the normal level as a result of removal of the pancreas, or the ingestion of excess of sugar.

In view of these findings it is not surprising that insulin causes reduction of the phosphates of the blood in normal rabbits (Wigglesworth, Woodrow, Winter and Smith) and in the blood and urine of diabetic patients (Blatherwick, Bell and Hill; Perlyzweig, Latham and Keefer, and Harrop and Benedict). Because of the possibility that a closer study of the exact time relationship of these changes in phosphates to those of other metabolites might throw light on the mechanism of the action of insulin Frank N. Allan and S. S. Sokhey have carried out investigations in which the urine of fasting, normal or diabetic dogs was collected by catheter at intervals of three hours throughout the day and of twelve hours during the night. The results of the analysis of these fractions are shown in the charts of figure 3, dog B, in which are given on the ordinates the hourly excretion of phosphorus (P) and of nitrogen (N) (in grams), of ammonia (NH_3) (in milligrams) and of total titratable acidity (T. A.) (in cubic centi-

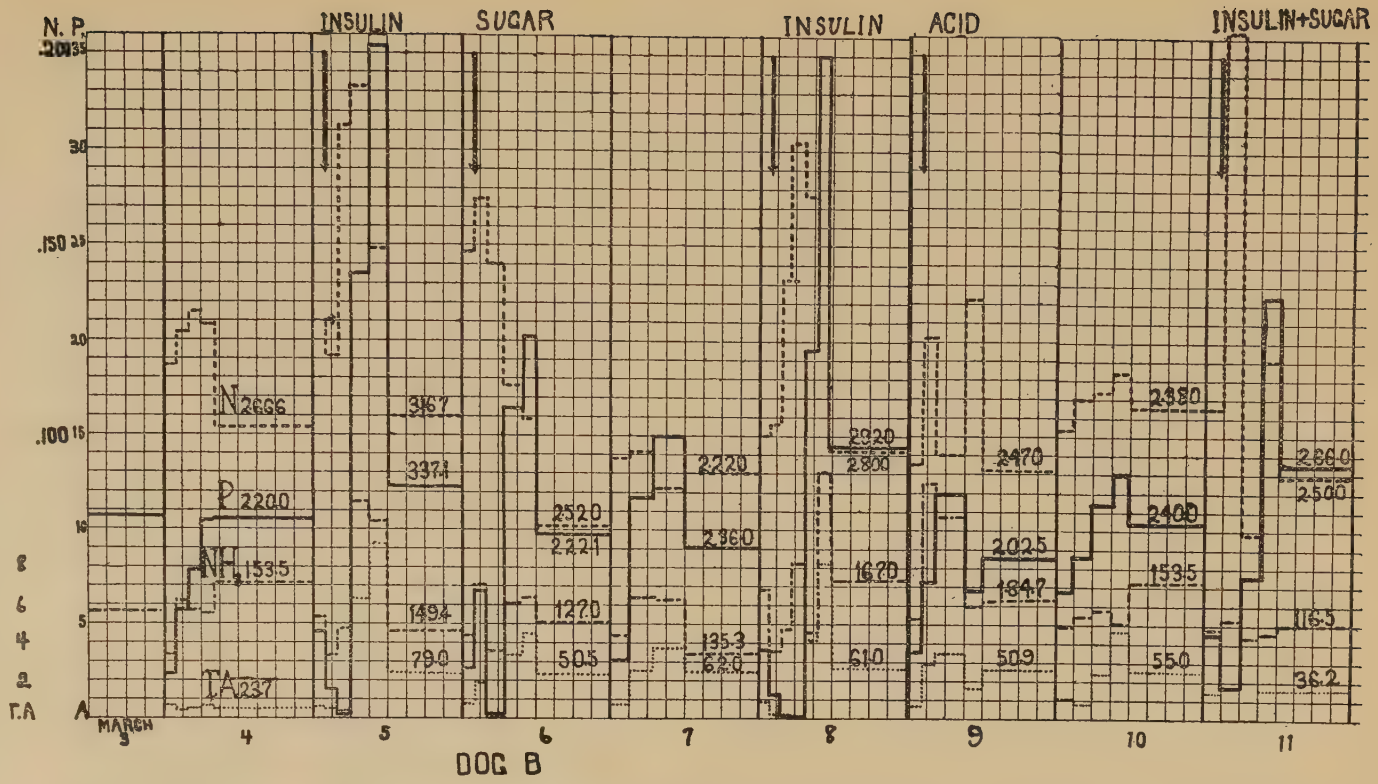


FIG. 3. CURVES REPRESENTING EXCRETION OF PHOSPHORUS, NITROGEN, AMMONIA AND ACIDITY IN THE URINE OF A DOG AT THREE-HOUR INTERVALS DURING THE DAY TO DEMONSTRATE THE EFFECT OF INSULIN, SUGAR AND ACID

meter 0.1 *N* acid). The abscissae indicate intervals of three hours each, the heavier lines indicating days. The figures written on the curves indicate the daily amounts of the various substances excreted, the day starting in each case at 10 a.m.

During the first day of the observations, which was the fourth since food was withheld, it is seen that the hourly excretion of nitrogen was higher during the day periods than during the night, that of phosphorus being lowest in the forenoon hours, reaching a maximum in the evening and being decidedly greater for the night than for the day hours. A pronounced change resulted on the following day when insulin was given in sufficient amount to cause the premonitory symptoms (lethargy, etc.) of hypoglycemia. During the 2 hours immediately following the injection (at 12 noon) when, therefore, the blood sugar must have been rapidly falling, the phosphorus excretion, instead of showing the usual afternoon rise, decreased almost to vanishing point accompanied by a fall in both ammonia and acidity. So far no change was observed in the nitrogen but in the next period of about two hours this increase rose very markedly, although phosphorus and total acidity had still further declined. In the third period, between the fourth and seventh hours following the insulin, a most remarkable increase occurred in the excretion of phosphorus, and the ammonia and acidity rose in sympathy. This increase in phosphorus and acidity continued during the next period but by now the nitrogen had begun to decline accompanied, to a certain degree, by the ammonia. By next morning the normal levels were practically regained but the total amounts, both of phosphorus and nitrogen, excreted during the twenty-four hours were much above the average for normal dogs. Repetition of this experiment, as on the eighth day in the present animal, gave the same general results and it could be observed that the volume of urine excreted was decidedly reduced during the period when the phosphorus was low and increased during the period when the phosphorus was high. Although, in general, the period of partial anuria corresponded to the development of hypoglycemia it was sometimes replaced by diuresis before the hypoglycemic symptoms had passed off.

When glucose was administered, as on the sixth day of the experi-

ment on dog B, results very similar to those following insulin were obtained with the significant differences that the excretion of nitrogen

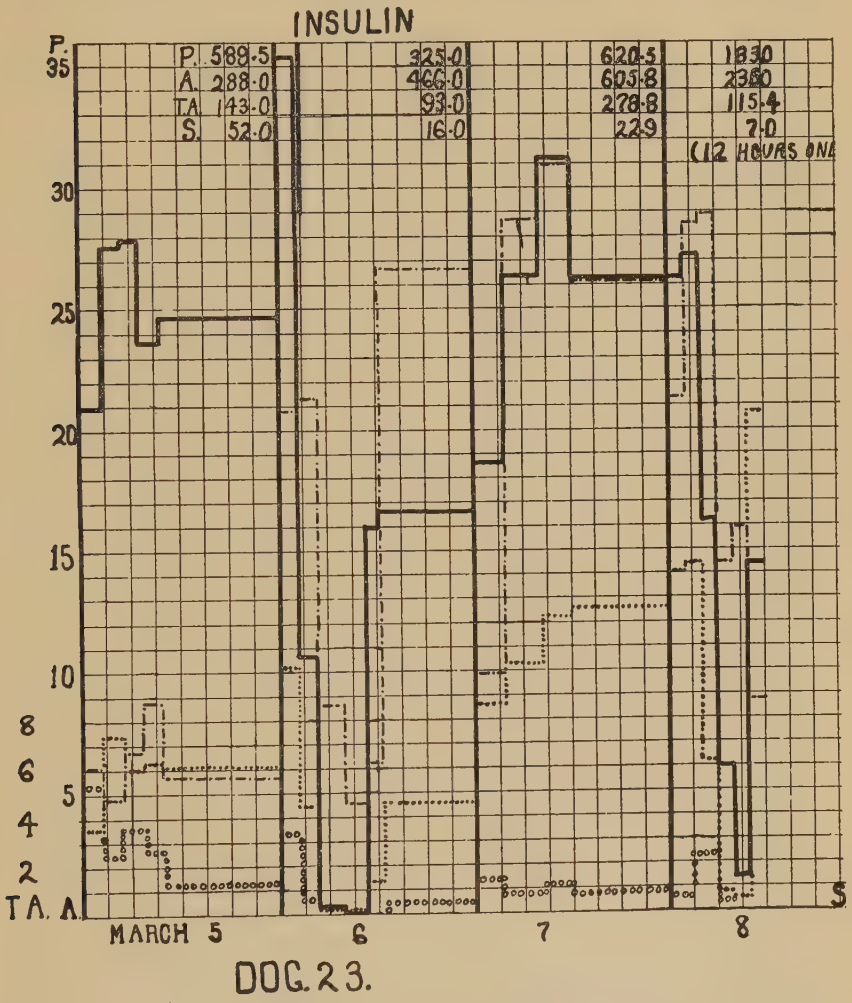


Fig. 4. Curves the Same as Those of Figure 3 Showing the Effect of Insulin in Diabetes

was not increased and the effects on phosphorus were decidedly delayed; thus, the decrease was not observed until the second period (of three hours) following the sugar.

It became of interest to see whether the repeated administration of insulin would have the effect of maintaining the suppression of the phosphorus excretion. A second dose of insulin was therefore given to another animal six hours after one which had been sufficient to cause decided symptoms, with the result that the phosphorus excretion remained suppressed for a further period of three hours. After this, however, the inevitable great increase occurred even although the animal was still obviously suffering from hypoglycemic symptoms. Before discussing the significance of these striking results it will be important to consider how other conditions affecting carbohydrate metabolism affect the excretion of phosphorus.

When diabetic (depancreatized) animals, were used the results shown in the curve of figure 4 were obtained. The dog had been depancreatized during several months being meanwhile kept alive by daily injections of insulin which were discontinued a couple of days preceding the observation. The average hourly excretion, on March 5 without insulin, was about double that of a normal animal of the same weight and when insulin was given, on March 6, the usual immediate decline in phosphates occurred. This was followed by an increase which is seen to have been much less marked than in normal animals, and indeed the total amount excreted in the twenty-four hours was found to be decidedly reduced, so as to approximate that of a normal animal of about the same weight. The excretion of nitrogen was markedly lessened and the sugar (line of small circles in curve) disappeared; as did also the ketone bodies.

The results on normal animals are probably dependent on stimulation of the internal secretion of insulin, as a result of the excess of sugar in the blood, and the question therefore arises whether administration of sugar to diabetic animals in which no endogenous production of insulin is possible would have the same effects. Attempts to show this have so far been frustrated by the very serious condition of acidosis into which the animals pass when their regular daily dose of insulin is withheld. The indications, however, are that the sugar has no effect.

This raises the question as to whether similar disturbances in phosphate excretion would be caused in other forms of experimental

hyperglycemia and glycosuria. The results of such observations are shown in the curve of figure 5 (dog I). Injection of 2 doses of 0.5 cc. each of adrenalin (on May 19) into a dog weighing 7 kgm. caused changes in the excretion of phosphorus very like those following insulin or glucose—an immediate fall followed by a marked rise—the excretion for the twenty-four hours being increased some 20 per cent

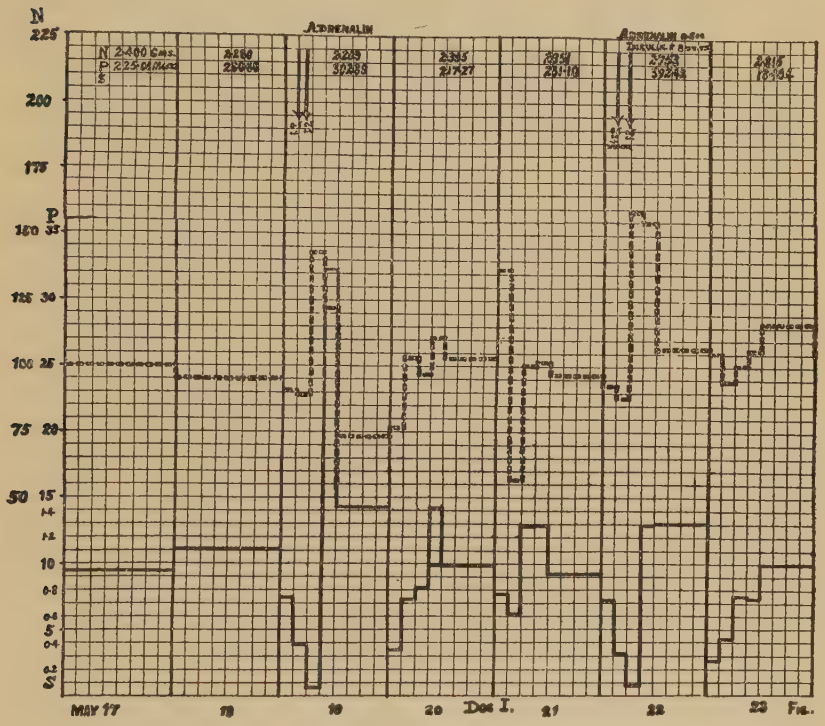


FIG. 5. CURVES SIMILAR TO THOSE OF FIGURES 3 AND 4 SHOWING THE EFFECT OF ADRENALIN

over the normal. The excretion of nitrogen became immediately raised while that of phosphorus was falling and then it declined to reach a subnormal level in about six hours after the injection, but on the succeeding two days a secondary increase was evident. In another animal following a massive dose of insulin this late increase in nitrogen was very pronounced. What then, it may be asked, was the effect

when insulin was given along with adrenalin? We have seen that it is possible, in glycogen-rich animals at least, to annul the hypoglycemic action of insulin by injecting adrenalin. Is this because the one hormone antidotes the other in their effects on carbohydrate metabolism, or does the adrenalin merely act because it adds "endogenous" glucose to the blood by causing excessive breakdown of glycogen? The results, as shown in the curve (May 22), indicate that the two hormones do not neutralize each other in their effects on the excretion of phosphorus. They cannot therefore be true antagonists.

Another form of experimental diabetes, namely, that due to phloridzin, was also investigated and the most striking results were those obtained on another dog (J) by twice daily injections during a period of four days. The results, as shown in figure 6 also, are most instructive. Immediately following the first injection the phosphates almost disappeared from the urine but they then rose steadily until on the fourth day nearly three times the normal amount was being excreted. On the days following the discontinuance of the injection the phosphate excretion became decidedly subnormal. Accompanying the increase in the excretion of phosphates there was a still greater increase in that of nitrogen so that it became more than doubled on the third day of the injections.

These facts are given in some detail since they appear to indicate one direction in which further exploration of the mysteries of carbohydrate metabolism is likely to be profitable. Why does diabetes occur when insulin is absent from the body and to what is the anti-diabetic influence of this hormone due? are the pressing questions awaiting solution. The results just detailed show that the metabolism of sugar is closely linked with that of phosphorus: obviously the two are interdependent in some way. Administration of insulin, or adrenalin, causes decrease followed by an increase in the excretion of phosphorus and when excess of sugar is given changes of a similar nature occur, but they are decidedly delayed. Evidently, therefore, it is not the concentration of sugar in the blood that is primarily responsible for the effects produced on the excretion of phosphorus. Furthermore, in the two forms of experimental diabetes which most closely simulate the clinical form of the disease, the phosphorus excretion becomes excessive

although in the one of them (due to pancreatectomy) hyperglycaemia is present, whereas in the other (due to phloridzin) the blood sugar, if anything, is subnormal in amount. Some process occurring independently of changes in blood sugar must be responsible for the changes, and this cannot be directly associated with an alteration in

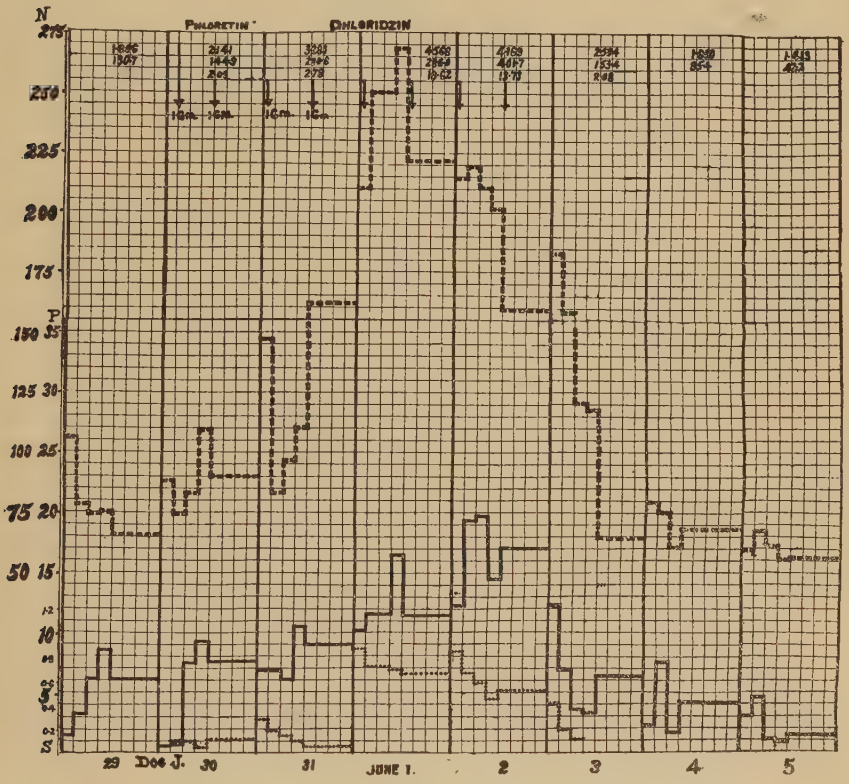


FIG. 6. CURVES SIMILAR TO THOSE OF PRECEDING FIGURES SHOWING THE EFFECT OF REPEATED INJECTIONS OF PHLORIDIZIN

the rate of combustion of glucose, at least in so far as can be judged from the behaviour of the respiratory quotient (see page 25) which may either be increased (adrenalin, sugar and, to a less extent, insulin) or decreased (pancreatectomy and phloridzin) while the phosphate excretion is falling and then rising. If we regard for the moment the

increase in phosphorus excretion it will be observed that this is pronounced in all cases except that following the administration of glucose. It is also related to changes in the excretion of nitrogen for with the exception of sugar injections a marked increase in the excretion of nitrogen occurs in all those cases in which the excretion of phosphorus is depressed. Is it possible then that the excessive phosphorus excretion is related to some process in which products of protein break-down are being dealt with in the body. In this connection it is worth noting that no change could be detected in the behaviour of creatinin following insulin, but that the excretion of ammonia became high relatively to that of total nitrogen.

Whatever may be the cause of the changes in phosphorus excretion, the assumption may be made that these occur in the tissues and are not merely changes in the rate of excretion by the kidneys of the inorganic phosphates of the blood. This has been demonstrated by finding that the inorganic phosphates of the blood become much depressed following injections of insulin or sugar. By examining samples of blood removed at frequent intervals from dogs injected with insulin, E. C. Noble has investigated the exact time relationships of the changes in blood sugar and phosphates. He has found that the two decline practically parallel to each other but that a decided rise, often of short duration, occurs in the sugar after the initial fall, without there being any change in phosphates. Otherwise, however, the two curves for several hours after the injection are remarkably parallel to one another indicating that phosphates and sugar must both have become retained in the tissues. Since it is well known that the production of compounds of glucose and phosphoric acid—hexose phosphates—are an important step in the breakdown process of glucose during alcoholic fermentation, it is natural to assume that the formation in the tissues of some such compound must be occurring to explain the disappearance of these two substances from the blood. Such a supposition would seem to receive some support when we consider the work of Embden and his collaborators who have given evidence to show that a compound of phosphoric acid with a complex yielding lactic acid (lactacidogen) undergoes decomposition as a result of muscular exercise.

In order to test this possibility we have, along with Eadie and Orr, determined by Embden's methods the inorganic and the lactacidogen phosphorus in the muscles of rabbits following the injection of large amounts of insulin and sugar but without finding any increase in lactacidogen, indeed rather a decrease. At the same time, however, we have in all cases been able to detect a decided decrease in the inorganic phosphates of the muscle although it is of course always very difficult to say what proportion of these may be derived from the blood necessarily present in the muscle.

CHAPTER VI

Physiological Assay of Insulin

A unit of insulin, as originally defined, is that amount which can lower the blood sugar of a normal rabbit weighing 2 kgm. to the convulsive level within four hours. More recently the definition has been modified to the extent that the animals must be deprived of food for twenty-four hours prior to being used—so as to reduce the glycogen stores to an approximately uniform low level. Since it was stated by some clinical observers that there are certain types of cases of diabetes in which less than one (physiological) unit of insulin as above defined is sufficient, it was decided, on their recommendation, to consider as one (clinical) unit for practical purposes one that was one-third of the above strength.[1] Even when precautions are taken to use animals of uniform size and breed, and to render them free of glycogen by more prolonged starvation than one day, the assays are, however, not strictly the same on different animals. To minimize the error thus incurred it is therefore necessary to use large numbers of animals and to base the final assay on the average of the results. In order to avoid the necessity of having to make the numerous blood-sugar estimations which this would entail, some observers have based their assays on the incidence of the well-characterized symptoms, on the assumption that these correspond to a definite lowering of blood sugar. This method has been used on rabbits in the Eli Lilly Laboratories, varying quantities of a given preparation of insulin being injected into a number of animals and the unitage calculated from the proportion which developed symptoms within a certain time. The method, however, is a costly one, and since it is evident if the development of symptoms is to form the sole basis for assay, that smaller animals than rabbits might be used, attention has been paid by D. R. Fraser (59), A.

[1] In this article, unless otherwise stated, one unit means the physiological and not the clinical unit.

Krogh, and H. H. Dale, and J. H. Burn (60) to the possibility of using mice. It has been found when these animals are injected with insulin and kept at room temperature that the most constant results are a profound fall in body temperature, and bodily weakness, so that the animal sprawls out on its belly, convulsive symptoms being only occasionally observed. If the fall of temperature be prevented by placing the animals in an incubator at 28°C., however, the symptoms are much more like those described for rabbits—convulsions, coma and paralysis of the legs being evident. By taking precautions to standardize the diet which is given prior to a short period of starvation (eight hours) and to use animals of similar age (varying from 16 to 20 grams in weight) a method of assay has been evolved in which one mouse unit is considered as the amount of insulin which will cause definite symptoms in 50 per cent of the injected animals (Krogh). At present certain difficulties make this method of assay unsatisfactory, but it is hoped that these may soon be overcome, since it is obvious that it would be of great value to be able to use mice in place of rabbits.

There are, however, several serious objections to the use of any method of assay that is based on the incidence of convulsions. The chief of these are: (1) that different animals, although of the same size, sex and breed, and in the same nutritional condition, are not necessarily of equal susceptibility to the development of symptoms, following the same dose of insulin; (2) that no consideration is taken of the duration of the hypoglycemic effect.

With regard to the first of these objections it should be pointed out that the symptoms make their appearance when the blood sugar has reached about 0.045 per cent, as originally stated by us, only when nonstarved rabbits are used. With starved animals, the blood sugar is usually considerably below 0.045 per cent when symptoms supervene (cf. McCormick, Macleod, O'Brien and Noble (61)). Thus, out of a total of 335 rabbits injected with insulin no symptoms were noted in 64 in which one or more of the blood sugars was decidedly below 0.040 per cent. On the other hand it is very seldom indeed that any symptoms are observed in starved animals before the blood sugar has reached 0.045 per cent (Macleod and Orr (62)). The relationship

between symptoms and blood sugar may therefore be correctly stated to the effect that they are likely to occur when the percentage of the latter has fallen to 0.045. In the light of more recent work it is probable that the frequency of symptoms at the higher levels of blood sugar, as observed by us in the earlier work, was due to the fact that the animals were not starved and therefore contained considerable stores of glycogen. By mobilization of glucose from these reserves, when the hypoglycemia reaches a certain critical level (see page 36), a further tendency to the development of hypoglycemia would be partially counteracted and the blood sugar thus held at a level (of about 0.045 per cent) at which toxic effects only slowly supervene. In starved animals, on the other hand, the blood sugar continues its rapid descent and goes below the level at which symptoms *may* appear before sufficient time has elapsed for the toxic condition to become developed.

The objection that no estimate is given of the duration of the hypoglycemic effect, when the assay is based on the incidence of symptoms, is of importance. As has been pointed out elsewhere in this article this duration depends very largely on the amount of glycogen stored in the body. Even if we could be certain that the glycogen had been reduced, by starvation, to the same extent in all the observed animals it would not necessarily follow that with different preparations of insulin the hypoglycemia must always be of the same duration. It is possible not only that the rate of absorption of insulin may vary, but also that its hypoglycemic action may be antagonized or delayed by the presence of extractives from the pancreas which have a hyperglycemic effect. In this connection it is of importance to remember that we have observed that extracts of the zymogenous pancreatic tissue of certain of the bony fishes causes an increase in blood sugar, islets being practically absent from this tissue but existing as separate glands (principal islets of Diamare and Rennie) in the mesentery (Macleod (29)). Collip (63) has also observed that insulin prepared by the usual methods from yeast, clams, etc., may not cause a marked degree of hypoglycemia until many hours after injection. It has also been our impression that impure preparations of insulin have a more prolonged hypoglycemic effect than those that are highly purified. For all these reasons, therefore, it is evident that the inci-

dence of convulsions is not likely to prove a suitable method upon which to base the accurate assay of insulin.

Before proceeding to discuss the method dependent upon the behavior of the blood sugar it may be well to point out further that one might have a preparation of insulin which contained, in 1 cc., an amount of insulin that was sufficient to cause a considerable reduction in blood sugar and yet not bring this to the convulsive level. Although such a relatively weak preparation might conceivably be assayed by the convulsive method, as by giving large injections, it is evident that the hypoglycemic effect could be arrived at much more satisfactorily by observing the behavior of the blood sugar.

The method of assay used at present by the Insulin Committee of the University of Toronto is carried out as follows: Normal blood is removed from the ear vein of each of 9 rabbits which have been starved for twenty-four hours, and the percentage of blood sugar is determined. No rabbit is used for the assay whose normal blood sugar is found to be below 0.105 or above 0.125 per cent. Into 1 of the rabbits is injected, subcutaneously, an amount of insulin which is expected to correspond to one physiological, or three clinical units. Into a second animal is injected an amount, about 50 per cent greater. The other 7 rabbits are injected with amounts varying from slightly below one unit to slightly below one-half unit. At intervals of one and a half, three, and five hours after injection about 1 cc. of blood is again removed from each of the rabbits and the blood sugar determined. The results are then calculated by the use of a formula which takes into consideration all features of the definition of a clinical unit, as well as allowing for the duration of the effect and for varying weights of the animals. This formula is:

$$\text{Clinical units per cubic centimeter} = \frac{a}{b} \times \frac{w}{c} \times 1.5$$

where a is the difference between the percentage of normal blood sugar and the average of the percentages of the blood sugars at one and a half three and five hours after injection; b is the difference between the percentage of normal blood sugar and 0.045; c is the number of cubic centimeters of insulin injected, and w is the weight of the rabbit in

kilograms. The factor 1.5 is used because the original (physiological) unit was based on the effect produced in a rabbit weighing 2 kgm. and the clinical unit is one-third of this (i.e., $\frac{2}{3}$). In several of its details the formula is more or less arbitrary. This is the case mainly with regard to the value of a, the other values b, c and w being required merely so that the assay may conform with the definition of a unit. Thus, the value a is taken as a measure of the average extent to which the blood sugar becomes lowered over a period of five hours following the injection of insulin. It might therefore be the same in two cases in one of which the blood sugar had quickly fallen to a low level with prompt recovery and in another in which the initial fall was not so steep but the recovery more prolonged. These differences are dependent, as has already been explained, partly on the purity of the insulin preparation, partly on its rate of absorption and partly on the fact that the mobilization of glucose from the glycogen stores of the liver is not necessarily the same in different animals, even when these have been starved for twenty-four hours. Probably the most important reason for this is that the liver in some of the animals will be devoid of glycogen whereas in others it will contain a small but varying amount. It is possible that starvation for a longer period preceding the injection—several days for example—might minimize this source of error but since this weakens the animals it would not be a justifiable procedure unless it decidedly minimized the errors and this, in our experience, is not the case. Even supposing the glycogen were equal in amount in different animals, another possible source of inconstancy in the rate of recovery of blood sugar is varying sensitivity of the controlling mechanism by which this recovery is brought about. When there is only a moderate decrease in blood sugar it is conceivable that the threshold level (of hypoglycemia) necessary to excite a marked increase in glycogenolysis is not reached, the recovery in blood sugar which does occur in such a case being dependent on the normal sugar production from the liver. On the other hand when the initial hypoglycemia occurs rapidly and is pronounced, hyperglycogenolysis becomes violently excited with the result that much glucose is added to the blood and recovery of blood sugar is therefore prompt.

Quite apart from these physiological errors there are others depend-

ent on the mathematical inaccuracy involved in taking the average of the blood sugars at one and a half, three and five hours. What we really desire to know is the extent of the area in the curves during which the blood sugar is below the normal level and it is clear that we do not accurately measure this by the above method. On the other hand, however, with such dissimilarity as exists in the results obtained on different animals towards insulin it is difficult to apply any other method of evaluation. The choice of the intervals for the first analysis of the blood sugar, following insulin, was based on the observation, along with G. S. Eadie (64), that the maximal influence of insulin in combating the development of hyperglycemia due to the injection of glucose (2 grams per kilogram body weight) is most marked when the glucose is injected in about one and a half hours following the insulin. The interval of five hours was chosen for the last analysis because it was found that by this time the effect of insulin, on starved animals, has usually disappeared, the three hour interval being chosen as intermediate between the two others. In the light of later experience it would probably be more accurate to make the first analysis in one hour after the injection since at this period the blood sugar in the majority of starved animals is at or near its lowest level. This modification is now being introduced but will not be formally adopted in the assays of the Insulin Committee unless it is found that by so doing a greater degree of accuracy is attained.

Another source of inaccuracy in the present method is dependent on the fact that it is assumed that the extent to which the blood sugar becomes lowered is directly proportional to the dose of insulin or, in other words, that the fall in blood sugar will be twice as great when the dose is doubled. This is certainly not the case since the action of insulin on the blood sugar, like that of epinephrin on the blood pressure (cf. Murray Lyon) obeys a logarithmic law, the effect of a unit becoming progressively less and less as the dosage is increased. It will be recalled that Frank N. Allan has shown a similar relationship to exist for the glucose equivalents of insulin on depancreatized dogs (page 32). We have endeavored to obtain adequate data from which to correct the present method used for the evaluation of a but without sufficient success to warrant the change. The reason for these difficul-

ties will be perfectly evident when the blood sugar curves of a number of starved rabbits injected with the same or with different doses of insulin are examined. Even when the same dose of the same insulin is injected, at weekly intervals, into the same rabbit the degree of hypoglycemia which results may not be the same (Macleod and Orr) so that it is hopeless to expect that varying doses will give dependable results. There are evidently certain factors involved in the reaction of an animal to insulin which we do not as yet understand and cannot therefore control. One of these may be related to the body temperature. It is significant that A. Krogh has found that in mice temperature greatly affects the susceptibility towards insulin (page 53) and we have noted that in rabbits the hypoglycemic condition supervenes more rapidly when the animals are kept warm. Even when care is taken to keep the rabbits under similar conditions with regard to the cooling condition of their environment, however, the effects of insulin are not uniform. It is possible that more uniform results will be obtained by using animals of the same breed, age and sex subjected to similar experimental conditions. We are at present investigating this possibility with standard white rats of the same litter.

It is realized, therefore, that the above factors make the evaluation of *a* a matter of considerable uncertainty so that means must be taken to minimize the error thus entailed in the final assay. This is done by employing a sufficient number of animals, and at present the practice is that if five out of the nine assays do not vary by more than 25 per cent an average of these five is taken as the final assay. Needless to say, if five out of nine assays do not correspond within these limits the assay is repeated until a majority do so. The error is then probably not more than 10 per cent between extremes. As a general rule the higher values are obtained when small amounts of insulin are used (*c* in formula) which of course indicates that the relationship between dosage and hypoglycemic effect is a logarithmic one (see page 33). Sometimes with the smaller doses a result is obtained that is very much higher than the average of the others of the same group. In such cases the assay is repeated on three more rabbits using this dose, and unless the result is duplicated the exceptional assay is disregarded. The present tendency in carrying out the assays is to use a limited

supply of rabbits, a record being kept of the exact behavior of each animal in previous assays. By so doing we are really making the assay by comparing the effect of an unknown sample of insulin against that of one whose effect on the same animal is already known. Although this probably gives more constant results these are not entirely satisfactory, for reasons which have already been discussed. These so-called "registered" animals are used for assay purposes once a week and it is of interest that they gain rapidly in weight and after some time begin to develop a decided resistance towards insulin, the blood sugar being lowered to a much less degree than previously was the case with the same dose, per kilogram body weight, of the same insulin. The occurrence of convulsions does not appear to interfere in the slightest degree with the well-being of the animals but nevertheless it is the practice to avoid, as much as possible, giving such doses as will cause them. The only way by which reliability of the assays can be tested is by comparing those made on different occasions from the same batch of insulin.

COMPARISON OF THE PHYSIOLOGICAL ASSAY WITH THE CLINICAL ACTION OF INSULIN

At first sight it might appear an easy matter to determine the number of grams of glucose which each unit of insulin could cause to be utilized by a diabetic patient, the so-called glucose equivalent. For reasons set forth elsewhere in this article, however this cannot be done unless the total dosage of insulin and the carbohydrate balance of the patient are taken into consideration and even then it is likely to be inconstant because of the varying endogenous production of insulin from what still remains of the patient's islet tissue. In a very general way it is usually considered that in cases of diabetes of moderate severity one clinical unit of insulin is capable of causing about 1.5 grams of glucose to be metabolized. Even at the risk of repetition it should be pointed out, however, that many more grams of sugar would be metabolized per unit when one unit of insulin is given to a patient excreting large quantities of sugar than when several units are given. With each added unit less and less glucose *per unit* would disappear from the urine. For these reasons, therefore, close corre-

spondence between the physiological assay and the clinical evaluation of the glucose equivalence of insulin, as this is ordinarily determined on diabetic patients, cannot be looked for. On depancreatized dogs, on the other hand, the two assays run closely parallel partly because there is no possibility of the endogenous production of insulin and partly because the dietetic conditions can be adequately controlled.

CHAPTER VII

Ultimate Fate of Depancreatized Dogs Treated by Insulin

The clinical history of the depancreatized dogs that were used for determination of the glucose equivalents (page 33) has revealed several facts of interest. As has already been stated these animals remained in excellent nutritive condition and usually gained somewhat in weight while on a diet of an excess of lean meat (500 to 600 grams daily) and cane sugar (100 to 150 grams daily). The only unphysiological condition observed, apart from glycosuria and hyperglycemia, was that only about one-half of the ingested protein was absorbed, as judged by the excretion of nitrogen in the urine. Of 3 such animals, 1 lived for two months, a second for four, and the third for seven months following the pancreatectomy. After these periods, in each case, symptoms of an acute breakdown in the hepatic function supervened—bile in the urine, jaundice, refusal to take food—and great bodily weakness soon developed, ending in the death of the animals within a few days of the onset of the symptoms. In all cases the liver was found at autopsy to be invaded by large quantities of fat—over 35 per cent of the moist weight being found in one case. On microscopic examination the fat was found to exist as very large globules, particularly in the cells of the portal area, giving the sections an appearance not unlike that of adipose tissue. In the few cells that contained relatively less fat, near the central vein, the protoplasm and nuclei showed some evidence of degeneration. The symptoms and the pathological findings strongly suggest the action of some highly toxic agency on the liver, but it is interesting that the kidneys of the 2 animals that lived four and seven months, respectively, showed no signs of toxic change, although such was observed in those of the animal which died in two months.

There are several possible causes for the toxic condition. It may be related to the faulty absorption of food, due to absence from the

intestine of the pancreatic juice. That protein was most imperfectly absorbed has already been stated and it is possible, as has also been suggested by Dr. Almon Fletcher, that the bacterial digestion of the unabsorbed protein might cause toxic decomposition products to be absorbed into the portal blood and so act injuriously on the liver cells. Lombroso (64a) has also noted that although the absorption, particularly of fat, becomes very imperfect in depancreatized dogs it is less impaired when some pancreatic tissue—a subcutaneous graft, for example,—is left in the body. McClure, Vincent and Pratt (64b) have denied this influence of pancreatic tissue on the efficiency of absorption of fat and have stated that this remains tolerably normal in the entire absence of pancreatic tissue from the body. We did not determine the extent of fat absorption in the above mentioned animals but we are certain that it was greatly impaired, it being necessary in order to keep them in good condition to remove as much fat as possible from the meat which was fed. It is possible, therefore, that in the entire absence of pancreatic tissue from the body there comes to be a deficiency of lipase and that this leads ultimately to a break down in the process of fat metabolism and accounts also for the faulty absorption of fat from the intestine. This proceeds with tolerable efficiency, when a pancreatic graft is present because some of the lipase carried by the blood finds its way through one or another of the secretions into the intestinal tract. Finally, however, it must be remembered that jaundice in dogs, if not due to obstruction of the larger bile ducts, or to blood changes, is believed to be invariably associated with degeneration of the hepatic cells which may have been due, in these experiments, to toxic substances derived from the bacterial decomposition of protein in the intestine.

The observations have therefore been repeated with the difference that raw pancreas has been substituted for part of the meat in the diet. So far no symptoms other than those from which any animals kept in confinement may suffer have developed in one animal kept now (November, 1924) for over a year and in another kept for seven months. It is probable that these beneficial results are due to the ferments contained in the pancreas for although it is likely that most

of the trypsin and lipase become destroyed through the action of pepsin in the stomach, some probably gains the intestine. The trypsin will then prevent bacterial decomposition of protein from becoming so predominant as to lead to the production of highly toxic amines and the lipase will cause the fats to be saponified and quickly absorbed. It is at least significant when raw pancreas is given that the faeces are much more normal and contain much less fat than when meat alone is fed. That the animals are really completely depancreatized is evidenced by the fact that omission of the daily administration of insulin is immediately followed by a great increase in the excretion of sugar and by the development of serious symptoms not unlike those of diabetic coma in man. In one of the animals which has put on considerable fat, withdrawal of the insulin causes much larger quantities of acetone bodies to be excreted in the urine than in the other, in which fat deposition is much less marked.

It is impossible to say whether it is because of the general improvement in intestinal digestion or because of the absorption into the blood of lipase or amylopsin from the fed pancreas that the beneficial results of pancreatic feeding are due. The lipase content of the blood serum of depancreatized as compared with normal dogs has been found by us to be increased rather than decreased. The method employed for measuring it was that of Rona and Doblin which consists in following with a stalagmometer the change produced in the surface tension of a saturated watery solution of triolein mixed with serum. The surface tension rises as the triolein becomes hydrolyzed and the rate of change is proportional to the lipase present. That any lipase is present in the serum of depancreatized animals indicates, of course, that the pancreas cannot be its only, or even its chief seat of manufacture in the body and that it is sometimes actually increased in these animals may be related to partial interference with the hepatic function, in which condition as Whipple has shown an excess of lipase appears in the blood.

With regard to the serum diastases after removal of the pancreas interesting results have been obtained by Markowitz. By the use of a method which was a slight modification of that of Myers and Killian, it was found in four depancreatized animals that decidedly less diastase

was present than in normal animals. In one animal the serum diastase was measured before and after pancreatectomy with the result that it fell to about one-half the pre-operative level in twenty-four hours after the operation and to about one-third in four days. Administration of insulin caused a slight increase but this may possibly have been due to a diminution in the rate of excretion of diastase by the urine.

The following abbreviated table shows typical results.

DATE (1924)	DIASTATIC POWER (Milligrams of sugar formed from 10 mgm. starch in 15 minutes at 37°C. less blood sugar)		BLOOD SUGAR	REMARKS
		(duplicates)	*per cent*	
March 10	153	146	0.092	Normal dog
March 11	143	149	0.098	Pancreatectomy after removing blood
March 12	75	77	0.385	
March 13	101	100	0.066	
March 14	55	58	0.348	
March 15	57	57	0.315	
March 16	49	47	0.325	
March 17 (3 p.m.)	46	44	0.300	
March 17 (11 p.m.)	66	71	0.092	8 hours after insulin
March 20 (12 n.)	55	55	0.500	
March 20 (3 p.m.)	64	64	0.054	4½ hours after insulin

These results stand in apparent contradiction to those obtained on diabetic patients in whom, as Myers and Cammidge have shown, the diastases are increased and, according to Myers, become lowered by insulin. Markowitz thinks that this may be related to the fact that the pancreas is still more or less functioning in the clinical condition.

PART II—CLINICAL SECTION

W. R. CAMPBELL

CHAPTER VIII

The Early Clinical Experiments

The experiments of Banting and Best in Toronto during the summer of 1921 were regarded with much interest by those conversant with them. The remarkable results of the crude extracts (19, 22), the product of their experiments, upon depancreatized animals early encouraged the hope that in due time the essential deficiencies produced by ablation of the pancreas in animals might be controlled, thus contributing vastly to our knowledge of the physiology of carbohydrate metabolism and furnishing a basis for a renewed attempt at treating human diabetics. How abundantly that hope has been fulfilled it is perhaps unnecessary to relate here. We can thankfully echo Joslin's words in the introduction to *diabetes* in Oxford Medicine—"'insulin is here!" May we also hope—to stay, or perhaps one day to be succeeded by one of its isomers or derivatives, robbed of certain of its limitations and with certain of its therapeutic properties enhanced.

For human physiology the crucial experiment must always be on man himself and in one sense the physician ranks as a physiologist of greater or less degree. But not alone is the physician desirous of knowing. His prime duty is to relieve, mayhap to cure, and experimentation on man is not justifiable without substantial hope of ultimate reward in knowledge or information conducive to that end. The splendid collaboration of the group of workers in the Department of Physiology swept the animal researches rapidly forward. When, by means of animal experiments, most of the essential points had been demonstrated, the Department of Medicine was requested in November, 1921, to test the pancreatic extracts in relieving human disease.

The supply of degenerated glands of dogs after pancreatic duct ligation and of fetal calf glands was quite insufficient to provide an

extensive trial in man of the extracts. For this purpose it became necessary to use extracts of adult beef pancreas, the uncertainty of the supply of which, coupled with the pressure of other physiological problems, delayed the actual clinical trial of the extracts until January 11, 1922. The first person to whom this latter extract was administered was a boy of fourteen years referred to the writer by Dr. Skeeles of Toronto. For a month prior to the actual administration the patient had been kept on a strict starvation diet. The records show that, while fasting, the blood sugar varied between 0.5 and 0.6 per cent. Sugar was continuously present in the urine and, indeed, the blood sugar level throughout the day scarcely varied. The patient exhibited ketosis to a marked degree. On January 11, after blood had been taken for sugar estimation, the pancreatic extract—a murky, light-brown liquid containing much sediment, which dissolved to a considerable extent on being warmed—was injected into the buttocks. The amount administered was 15 cc., a dosage calculated as being one-half as much as would give a definite reduction in blood sugar in a depancreatized dog of equal weight. Somewhat to our disappointment the blood sugar level was reduced by only 25 per cent. Looking back one can see as well a slight fall in sugar excretion, but at the time this was too small to be convincing.

Production of sterile abscesses in the first patients to whom the extract was administered made it imperative that the mixture should be rendered protein free. The desired result was accomplished by Collip who, by precipitation of the insulin, was also able to supply stronger extracts not containing the large amounts of salt and protein which in the earlier extracts had caused the patients to complain of a persistent burning sensation. The chemical conditions essential for production of this extract were not well understood and at this time none of the patients received nearly adequate treatment.

Various points were investigated in different patients and sufficient data obtained to justify our preliminary statements (30, 65) regarding the effect produced on some of the fundamental phenomena of diabetes mellitus by treatment with these extracts, namely: that blood sugar can be reduced to normal values; glycosuria can be abolished; the acetone bodies can be made to disappear; the

respiratory quotient can be made to rise decidedly and the patients themselves to remark their improvement. At this date, moreover, the comparatively short duration of the action of the extract, the occurrence of toxic reactions and the limitation of its value to certain types of diabetes were referred to.

Meanwhile, through the work of a team of workers (23, 24, 66, 35, 32, 67) in the departments of Physiology and Pathological Chemistry, the problems of standardization of insulin and its effects on laboratory animals were prosecuted diligently. As a result it was found that the lowering of the blood sugar, which was first observed by Collip to occur in normal rabbits, could be made the basis of assay. It was also found that the peculiar toxic symptoms which supervened after large doses of insulin were dependent upon the hypoglycemia and could be immediately antidoted by glucose. Coördinated rapid solution of particular problems, coupled with prompt communication of the results to all members of the group, encouraged all to believe that the individual difficulty confronting each worker would soon be surmounted and to hope for the ultimate production of sufficient extract to undertake more detailed investigation of the problem in man.

Shortly after the publication of the preliminary clinical report an attempt was made to produce insulin on a larger scale. Unfortunately, though small quantities could be obtained by reverting to the experimental laboratory apparatus, a great many failures resulted before the larger sized apparatus gave practical yields, and the clinical work by the Department of Medicine was virtually discontinued for a time.

During the summer of 1922 investigation of insulin was started in the Christie Street Military Hospital and in the Hospital for Sick Children, Toronto, by Dr. F. G. Banting, and recommenced in the Department of Medicine of the Toronto General Hospital. As soon as it became possible to obtain pancreatic extract, or insulin as it was now called, for additional patients the most severe cases were admitted and treated. Those who through circumstances were unable to pay, received treatment in the public wards of the Toronto General Hospital, while an equal number of the more affluent were

treated in wards especially reserved for them. By this means it became possible to limit our attention to a series of most severe diabetics who not only needed the insulin the most but also furnished the most searching test of its efficiency. The patients all realized that they were embarking on an experiment which might be of great benefit not only to themselves but to other sufferers from the disease and that a most strict adherence to the minutiae of treatment was necessary if the results were to be of any value. To their credit it may be said that I have not previously experienced such satisfactory coöperation on the part of patients. Thanks are due to the authorities of the Toronto General Hospital, who provided special nurses, extra dietitians, assistants and supplies sufficient to carry out this investigation and coöperated in every possible way to make it a success.

We were certain that, if insulin were properly applied, a new chapter in the treatment of diabetes would be opened. How to prevent it from being exploited and, through ill-advised treatment, from falling into disrepute was a problem which the Insulin Committee solved by placing it in the hands of some of the eminent specialists on diabetes in the United States. Owing to the supplies being limited at first it was necessary to restrict its distribution to a few, but later the numbers investigating its use were gradually expanded as the production of insulin increased. To these, our collaborators, we are grateful for their kindly assistance and loyal support. Among so many with somewhat differing views regarding diabetes, there have naturally arisen differences of opinion as to methods of treatment, but underlying all these is a fundamental confirmation of our original thesis (30, 65), which has firmly established the therapeutic value of the drug.

The second clinical paper (68) on insulin was based on experience derived from the treatment of more than 50 patients with severe diabetes. In general it may be said that the results of the treatment of the larger number of cases completely confirmed the tentative conclusions reached in the preliminary paper. Adequate supplies of insulin permitted a much more prolonged trial in a number of individuals and showed that no untoward effects need be an-

ticipated from its continued use. Glycosuria was successfully controlled and the blood sugar maintained at normal levels for long periods. The acetone bodies were burned under the influence of the insulin and many cases of severe acidosis recovered. Six patients in whom complete diabetic coma had developed recovered after its use, while four died, one due to insulin shortage and the other three to complications. Uncertainty of standardization, deterioration of extracts, as well as imperfect balance between insulin and ingested carbohydrate gave rise to a considerable number of peculiar reactions associated with hypoglycemia in patients under insulin treatment. This condition in man, which in many ways resembles the hypoglycemic state in animals, was studied and described together with its treatment.

Notwithstanding the excellent control of the chemical phenomena of diabetes the greatest interest centers in the improvement in the general condition, mental and physical, of the patient. In these severe cases the improvement was remarkable and can only be compared to that produced by another internal secretion—thyroxin in myxedema cases. The mental state of hopeless, irritable depression, almost melancholia, characteristic of the advanced, emaciated diabetic gives way to a spirit of cheerfulness and optimism. Insomnia becomes less troublesome and interest in his surroundings is reawakened. The feeling of lassitude or early exhaustion after slight exercise disappears. The carriage of the patient improves and physical vigor is gradually restored. Thirst is no longer excessive and a state of continuous hunger is replaced by a sense of comforting fulness with an appetite for meals. The body weight can be caused to increase at will and many of the patients in a very short time have been able to return to their former work. In the case of patients with infections insulin was found to confer a definite benefit. A number of suggestions as to the use of insulin in treatment are incorporated in the paper.

In the two earlier papers a number of points received only brief mention. More detailed presentation of the results of the investigation of insulin appeared with the papers of our earlier collaborators in the November–December, 1922, number of the Journal of Meta-

bolic Research. The succeeding pages will be concerned largely with a review of these papers (69, 34, 70, 71, 45, 72, 73, 74, 46, 75) since in them is to be found first reference to the effect of insulin on certain phenomena of diabetes. To many other authors we are indebted for confirmatory data which it is not possible to review in detail.

GENERAL INFORMATION

Insulin, a substance widely distributed throughout the animal kingdom, is usually derived from the pancreas of mammals or fishes. Its function is to promote the conbustion of carbohydrates. It is obtainable commercially as a sterile standardized solution in various strengths, 5, 10, 20, 40 and 80 units per cubic centimeter. It also can be prepared in the form of hypodermic tablets (Krogh, McCormick and Noble (60)). Apart from the decreased cost it may be expected that these will prove of value because of their greater stability especially in very cold or very hot climates. Under ordinary conditions of temperature insulin solutions are stable for long periods without especial precautions. The physiological assay of insulin is discussed in the first part of this paper and hereinafter the clinical unit is the unit of measurement of the hormone.

ADMINISTRATION OF INSULIN

Insulin, as was shown by Banting and Best in their original communications (19, 22), is easily destroyed by incubation with pancreatic juice. Peptic activity likewise rapidly destroys its action. Tests of insulin administered by mouth have been made by Banting, by Woodyatt (46) and by Joslin (71) with negative or almost negative results. The slight and variable activity found in some instances when given by this pathway is probably dependent upon early absorption of a portion of an enormous dose. Woodyatt (46) also conducted experiments in which oral, rectal, vaginal and intranasal administrations were given as well as inunctions. These methods yielded very weak, doubtful or negative results. My own experiments (unpublished) with insulin by inunction show a slight activity of the substance when administered in enormous doses.

Telfer (76), in rabbits, obtained positive results after rubbing insulin into the shaved skin of the animal. These results have been duplicated by Macleod and McCormick (60). The procedure deserves further investigation, both as a means of prolonging the action of insulin and also as a method of producing a quite definite feeling of well-being in some patients who do not show distinct evidence of requiring insulin. For this purpose a much cheaper and less refined preparation could be used.

In the average case of diabetes insulin is best administered hypodermically. The intravenous method is only used to obtain rapid effects in cases suffering from diabetic coma. The needle should be fine and very sharp—$\frac{7}{8}$ inches 27 to 29 gauge needles are the best—and the insulin injected through cleaned skin into the subcutaneous tissue. A little pressure may be used to numb the skin but great care should be taken to cause as little trauma as possible. Particular attention should be given to the introduction of the needle into loose subcutaneous tissue. Any part of the body where this is available is suitable; pressure points should be avoided. Insulin must not be injected into the skin as marked redness and stinging and sometimes, in the emaciated patient, necrosis of the skin develops. In all probability this is due to the preservative used. The injection must not be made into the muscle tissue as it is not only painful but gives rise to swelling and long continued induration. Bowie and Robinson (77) have shown that degeneration of the muscle fibres with a leucocytic invasion occurs in such areas. Similar microscopic appearances are presented by many other substances injected into muscle. The ultimate condition appears to be fibrosis in the muscle.

The time of administration of insulin is important in relation to the size of the dose and the efficiency with which it supplements the internal secretion of the patient's pancreas. Under normal conditions the blood sugar in man is maintained at relatively constant levels save for periods following meals, during which food is being absorbed. Coinciding with this we have, in all probability, a continuous production of insulin with a peak of production at the period of absorption of carbohydrate. In cases of mild diabetes these latter

periods are the only ones in which the production is likely to prove insufficient so that glycosuria results. With severe diabetes glycosuria is constant, though the percentage excreted after meals is higher than at other periods of the twenty-four hours. In using insulin it would, of course, be ideal if it could be supplied so as to imitate the natural process but this would mean continuous injections or adoption of some method of delaying absorption. Experience has shown that insulin can develop its full therapeutic value when it is given at any time of the day provided a suitable amount is used for the particular needs of the individual. For the large majority of patients, however, insulin is best given in the half hour just previous to meals. This permits the insulin to neutralize the hyperglycemic effect of the meal. In most cases, with diets containing somewhat less than one-third of the carbohydrate in the breakfast, one-third in the noon meal and the remainder in the evening meal, it is possible to divide the insulin into two equal doses and administer these before breakfast and before the evening meal.

In certain patients, however, the proportion of the insulin required at each injection may not be the same, and it has to be remembered that hypoglycemia must be avoided just as carefully as hyperglycemia and glycosuria. The morning dose of insulin given when the blood sugar is at the fasting level is absorbed in sufficient time to prevent glycosuria as a result of breakfast, and the latter delays the fall of blood sugar due to the insulin. When minor hypoglycemic reactions do occur they are most often noted at 11:30 a.m. to 12:00 noon, and are quickly antidoted by any easily absorbable carbohydrates present in the noon meal. Lyon's (78) apparently different results are, I believe, dependent upon the fact that he permits high morning fasting blood sugars so that glycosuria occurs when the insulin is given at the same time as the meals. He recommends insulin two hours before meals. This is an inconvenience which should be avoided in the case of most patients.

The period from the evening meal to breakfast is the longest time elapsing without replenishment of the carbohydrate supply. Provided sufficient insulin is available when energy is required, carbohydrate is burned in preference to other foods. This process may use up the

supply of carbohydrate and leave only fat and protein to be burned during the early morning hours. It is not unusual for a slight ketonuria to develop at this time. The same process might cause a greater liability to hypoglycemia during this period and this condition might be very dangerous if it occurred during sleep. For these reasons a larger portion of the carbohydrate is prescribed in the evening meal.

Should the insulin requirement exceed forty to fifty units it is usually better to divide the day's allowance into three or more doses. Unless these patients are receiving diets quite high in total glucose they will usually be quite severe cases with little or practically no tolerance for carbohydrate, and the most suitable time for injecting the doses may require very careful investigation. Often they may be given just before each meal, though the quantities should not be equal at each meal.

The practical utility of a method in which but one dose of insulin is administered daily has led Fletcher and the writer on many occasions to test its efficiency. When large doses must be given this method is unsuitable since the patients develop hypoglycemia more often, and when the relatively short period of the action of insulin has passed, hyperglycemia, and often glycosuria, develops. With one dose, also, the total amount of carbohydrate burned is less than with several doses. The carbohydrate equivalent of small doses of insulin has also been shown by Dr. Frank Allan (43), working in Professor Macleod's laboratory, to be decidedly greater than when larger doses are given. Dr. Frederick M. Allen's (75) objection may be quoted: "Even if all food in excess of the patient's tolerance be added to a single meal following this injection the fact remains that this food is only partially burned at the time and is largely stored as glycogen and other reserves which create demands for insulin after the single dose is used up." He favors two doses in the milder cases, three (before each meal) in the more severe, and four (i.e. every six hours) in the most severe cases. In connection with the last class of diabetic it should be noted that, in one most severe case apparently with zero tolerance, insulin was given as often as every four hours.

Other investigators have administered insulin somewhat differently. Fitz, Murphy and Grant (73) give it two to three times daily, an

hour to an hour and a half before meals. Williams (72) has included charts in his article showing the superiority of three doses of insulin daily. Woodyatt (46) expresses the view that one injection daily is sufficient in 90 per cent of his cases, though occasionally two doses are employed. Wilder (45) believes that maximal results are obtained with a single injection, thirty minutes before breakfast. Barborka (79), writing later from the Mayo Clinic, favors a single dose when this does not exceed thirty units per day, and twenty-five units before breakfast with the remainder of the insulin at 3:00 p.m. if more than thirty units are necessary. Joslin (71) and his associates make use of two doses of insulin before breakfast and supper in the majority of their cases.

We have not been able to obtain satisfactory results with the single dose method when the daily requirement exceeds ten units. Objection has already been taken to some of the methods mentioned above on theoretical or practical grounds. These objections are obviously founded on ideals of treatment of the diabetic. Since there is not uniformity of opinion among the various groups of workers who have used insulin, with regard to methods of administration, it may be of service to note here the general principles which have guided the treatment as given in Toronto. In the opinion of the writer these include the principle of adequate nutrition and sufficient food on which to do light work since, failing cure, this alone accomplishes the maximum result—conversion of the patient into an economic asset. Adequate rest to the pancreas is essential to prevent deterioration of tolerance and can only be accomplished by keeping the patient aglycosuric and his blood sugar reasonably near the normal level. Excessive caloric intake in all diabetics should be discouraged. Maintenance of patients at or 10 per cent below the normal weight is desirable. For many cases insulin will be necessary to accomplish these results but for a very considerable proportion of patients dietetic treatment alone is necessary.

The fundamental principle underlying treatment is thus a therapeutic one and we are the less concerned over the question of undernutrition since insulin can be used to replace the wanting endogenous secretion of the pancreas in those patients who previously could

not be made aglycosuric without subjecting them to marked under-nutrition. That marked under-nutrition possesses any mysterious benefits for the patient who has sufficient tolerance, after eight years' use and observation of the method, I frankly do not believe. Why it should now be employed when insulin is available is not clear. Arguments based on the markedly increased amount of insulin required for maintenance of a patient aglycosuric when on higher diets are wholly fallacious since they take no account of the chemical law underlying the action of insulin. (See preceding pages (Frank Allen, pp. 31 et seq.).)

SENSITIZATION TO INSULIN

In the earliest preparations sensitization to the proteins of the particular animal furnishing the pancreas was to be feared and, when our first patient returned to us in a state of severe acidosis bordering on coma with very marked dehydration, considerable care was taken to avoid producing an anaphylactic reaction. Desensitization precautions (Besredka method) were used. Fortunately no evidence of sensitization has appeared in this patient, though it is now three years since pancreatic extract was first given, and insulin has been given daily during the last 27 months. In the large majority of patients sensitization phenomena have been entirely absent. The occasional case, however, has sometimes shown a slight urticaria and, indeed, one particular batch of insulin, produced in the hottest part of last summer, showed particularly irritant qualities for a number of patients. Much more rarely marked swelling, itching, wheals, or even pain has been produced. Local applications of saturated magnesium sulphate solution, saturated soda bicarbonate solution and 1 per cent phenol have given local relief in these cases. Adrenalin has been tried with temporary success. Calcium chloride internally has not proved of value. One's impression is that these phenomena are steadily diminishing in number with the increasing purity of the insulin.

Sometimes, however, patients continue to show these sensitization phenomena even when the purest insulin obtainable is used. In

such cases insulin should be obtained from another source or desensitization methods, as applied to hay fever sufferers, should be tried. There may be, however, a residual group who will respond to any hypodermatic medication, protein or not, with phenomena simulating the allergic type. These cases, which Professor Macleod is inclined to regard as a sensitized reflex rather than true allergy, will probably be merely of a local nature. Thus far we have not had to deal with such a case. Williams (72) has reported a case of sensitization to insulin with very marked symptoms—swelling of the lips, urticaria, wheals and very marked weakness and prolonged prostration, and finally, exfoliation of the skin occurring on the substitution of one make of insulin for another. The lungs and heart were not affected. Continuance of the insulin originally used has not induced sensitivity to beef insulin.

Geyelin (74) mentions mild serum sickness in 3 children, with successful desensitization to the insulin in 2 cases; the third apparently being very mild and clearing up spontaneously. Wilder (45) and his associates record severe protein reactions with 3 cases treated with the earlier preparations: urticarial rashes, nausea, vomiting, epigastric pain, diarrhea and profuse sweating are noted, together with reddening of the eyes, puffiness of the face and alterations in pulse volume and heart rate. As illustrating the idiosyncrasy of patients one of Wilder's cases received a small dose of a certain preparation which caused severe anaphylactic symptoms. We employed 120 cc. of the same solution, which was of low potency, intravenously in one dose in a coma case without deleterious effect. The patient recovered. Joslin (71) also mentions four protein reactions. None of our cases have had protein reactions so severe as those noted above. Their possible occurrence, however, should be remembered by anyone becoming responsible for insulin treatment in a diabetic.

CARBOHYDRATE EQUIVALENT OF INSULIN

The undoubted value of insulin as a therapeutic agent has led to attempts at assaying the unit in terms of carbohydrate metabolized. This problem was first attacked from the clinical side since its practical

importance is so great. The most illuminating and valuable work, however, is that done in Professor Macleod's laboratory by Dr. Frank Allan (43), working with depancreatized animals. This has already been fully discussed by Professor Macleod in the preceding pages. Particularly suggestive is the formula developed since it corresponds to the law of enzyme action. Also the form of the curve helps to explain the clinical results obtained since all those presenting data on the subject are making use of a very similar type of diet, while those denying the possibility have employed most erratic dietetic procedures. That it makes a difference from whence the sugar is derived, all will agree. Wilder (45) has specifically stated that strict adherence to low protein diets increases the reliability of the results.

On *a priori* grounds the appraisal of the carbohydrate equivalent of insulin in clinical cases can never be wholly satisfactory. The patient, unlike a totally depancreatized animal, may possibly show fluctuations in the endogenous insulin production from time to time. Extraneous factors also play a part. Early or mild cases are not dependable. Desugarization may result in a rising insulin production. Woodyatt (46) selected cases with long metabolic records with relatively fixed tolerance and placed them on regimes which permitted the steady excretion of 20 to 30 grams of glucose daily. The insulin was then administered and the decrease in glucose excreted divided by the number of units gave the burning power of insulin per unit. A confirmatory test, discontinuing the insulin and determining the glucose excretion, was then performed to make sure there was no increased endogenous insulin production.

Wilder (45) also used selected patients, free from infections or other complications, placed on a basal maintenance food mixture. Average results of several days were used. The patients always showed appreciable glycosuria. The basal tolerance was determined by subtracting the amount of glucose excreted from the total glucose value of the diet and the diet then increased a definite amount for several days until sugar and nitrogen output became reasonably uniform. Insulin was then administered and the amount of additional glucose metabolized credited to the insulin administered. According to this method the unit assays between 1 and 1.5.

The precautions suggested by the above writers in determining carbohydrate equivalents are well taken. In Toronto the problem has been approached a little differently though the results are of the same general order. In fact when allowance is made for the fact that the insulin used by these workers (Iletin) was of lower unit value than that used in Toronto, Wilder's (45) results are the same as Campbell and Fletcher's (80). Woodyatt's (46) results are a little lower but this may be explained by the fact that he makes use of 1 gram of protein per kilogram of body weight, whereas both Wilder and ourselves have used two-thirds of a gram of protein per kilogram body weight. Dr. Frank Allan's results seem to indicate that a lower carbohydrate equivalent would result when protein constitutes a high proportion of the total calories.

The carbohydrate equivalent of insulin seemed to us meaningless except from the therapeutic standpoint in relation to a particular type of treatment. As, in Toronto, the abolition of glycosuria and the maintenance of normal blood sugar was regarded as an essential in adequate treatment of the disease it seemed of value to learn the power of insulin to induce glucose combustion under these conditions. It was early noted that marked arteriosclerotics gave discordant values. Infection in a diabetic, the presence of acidosis, of emaciation or dehydration, also high thresholds of excretion for glucose were found to disqualify patients for testing purposes. To avoid inclusion of the effect of a spontaneously rising tolerance for carbohydrate it is necessary to keep the patient a sufficient period of time on a definite diet to show that this factor is absent. The diet was increased and the amount of insulin required to balance the extra carbohydrate and to bring the blood sugar to the same level then determined. The total extra glucose divided by units of insulin then corresponds to the carbohydrate equivalent of insulin. In applying this method, however, it was found that the result was practically identical with that obtained by dividing the difference between the tolerance for carbohydrate on a basal diet and the total glucose of the diet (the number of grams of glucose excreted) by the number of units of insulin used to maintain the patient sugar-free. The results, using batches of insulin with assay of which we were reasonably

sure, gave an average value for the carbohydrate equivalent of 2.2 grams per unit. In a series of fifty-three mild diabetics Joslin (81) found the average carbohydrate equivalent to be 2 grams per unit (Joslin, ed. iii, p. 41). Major (82) also finds the same value.

The clinical significance of knowing the glucose equivalent lies in the fact that most patients treated on the usual types of diet can be given a dose of insulin calculated so as to make them aglycosuric and can then be maintained in this condition by a somewhat smaller dose. Thus, the average number of grams of glucose excreted on a diet supplying the basal requirement in calories divided by 1.5[1] gives the dose of insulin required for rendering the patient aglycosuric. $\frac{\textit{Grams glucose excreted}}{2.2}$ gives the average dose of insulin required to maintain the patient sugar-free in the absence of other complicating factors. By application of these principles much of the usual, prolonged and elaborate methods of treatment become unnecessary. Certain cases when treated according to these principles may become sugar-free but not attain suitable fasting blood sugar levels, and it becomes necessary to add two units of insulin to the daily dose for each 0.01 per cent if it is desired to lower the blood sugar. A variation in this rule is useful in judging the increase in diet allowable in a patient on dietetic treatment. If, for instance, the blood sugar level is 0.08 per cent it will not become excessively high (over 0.12 per cent) if 10 grams of carbos and 40 grams of fat are added. (The total glucose in such an increase is 10 + 10 per cent of 40 = 14 grams; $\frac{14}{2}$ = seven units required to metabolize the increase; $\frac{7}{2}$ = 0.035 per cent = maximum increase in blood sugar produced by the addition to the diet.)

[1] This factor is derived from experience. It may be suggested that the excess insulin (50 per cent) over and above the carbohydrate equivalent of the glucose excreted is used to metabolize the excess blood and tissue sugar. Suppose the blood sugar in a 60 kgm. diabetic is 0.3 per cent, i.e., 0.2 per cent above the normal. The tissue sugar is somewhat less than this level (according to the work of Palmer (83)), say 0.1 per cent above normal. In such an instance the body would contain 60 grams of sugar, requiring insulin for its metabolism. There are, however, many other possibilities open; e.g., the endogenous production of insulin may decrease when the stimulation due to the overload is removed. In any case the dose of insulin must be promptly reduced to a lower value when the patient becomes sugar-free.

Sherrill (84), in a long paper, assembles evidence to demonstrate that, under widely varying conditions, the carbohydrate equivalent of insulin shows very marked differences not only in different patients but also in the same patient under different conditions. He also states that glycosuria and insulin requirement are governed to a very important degree by the total caloric value of the diet. No especially powerful glycosuric influence of protein, either because of its specific dynamic action or supposed toxic action, was found.

Frederick M. Allen (85) also discusses the insulin requirements under various conditions, particularly the amount of fat used and the total calories in the diet. He believes that the insulin requirement of the organism is governed by carbohydrate, fat and all other elements entering into the diet or metabolism. The need for insulin is related quantitatively to the body mass as well as the amount of food to be metabolized. These observations support the belief that insulin is the true internal secretion of the pancreas. The under-nutrition treatment of diabetes as opposed to other dietary procedures, is held to be justified. Credit must be given Allen and Sherrill for assembling such a mass of data showing the variation in carbohydrate equivalent under different conditions. It is, in a way, confirmatory of the work of Frank Allan, referred to above. As the carbohydrate equivalent of insulin in man was determined for the purpose of a systematic treatment of diabetes and it was recognized that varying the conditions altered or abolished its value, the polemical character of these papers seems to be unjustified. That the insulin requirement is related to body mass as well as the food to be metabolized is a broad deduction from the evidence presented. The interrelationship between the numerous factors with which insulin is associated will, it is hoped, become much clearer as the result of investigations now proceeding. In the meantime Allen and Sherrill's results are quite consistent with chemical laws, such as the mass law and the law of enzyme action.

CHAPTER IX

Effects of Insulin on Metabolism

Many investigators have contributed information of value in regard to the alterations of the metabolism of diabetics under insulin. Interpretation of some of the results is by no means simple in the present state of our knowledge and it is not assisted by the fact that some investigators have employed their results mainly as arguments for some particular theory regarding the cause or treatment of diabetes.

RESPIRATORY METABOLISM

Particularly interesting are the results on the respiratory metabolism, though these must be interpreted with the greatest care. So many fallacies arise in this work that, in all probability, we must await the results of a prolonged study of the complete metabolism of a severe diabetic in a chamber calorimeter before all details can be elucidated. Quite apart from technical errors of analysis, such details as the physical condition of the patient, over-breathing, the presence or absence of acidosis, dehydration, infections or other complications, the duration and severity of the disease, the protein, fat and carbohydrate stores of the body, together with the influence of food, will have a marked influence on the result. Without doubt, some of the discrepancies noted are due to these factors. The psychic factor is so obviously important that all investigators have endeavoured to rule it out, but the fact remains that insulin causes such a marked change in the mental state and the physical vigor of the patient that it is difficult entirely to accomplish this.

Some preliminary observations made in Toronto (30) on severe diabetics, showed a rise in the respiratory quotient from 0.72 to 0.91 and 0.94 and similar values, after administration of insulin. This, alone with observations on diabetic dogs (35), was accepted as a part of the evidence that insulin actually causes combustion of carbo-

hydrate in the diabetic organisms. Having established this fact, it was not considered advisable to continue further with the respiratory studies in Toronto since to do so on an adequate scale would have entailed a greater expenditure of time than seemed advisable in face of the many other problems that awaited investigation, especially since others investigating the action of insulin, such as Wilder, Boothby and Joslin, were in a more favorable position to prosecute work in this field.

Wilder, Boothby and their associates (45) investigated the behavior of the respiratory quotients of two diabetic patients when given glucose or levulose, with and without insulin. When glucose was given without insulin no rise in respiratory quotient occurred and, indeed, a slight fall is recorded in one of the cases. With levulose alone there was a distinct and immediate rise in the respiratory quotient though to a less extent than in normal persons.

With glucose and insulin a definite though delayed increase was observed in the respiratory quotient in one case; in another the increase was within the limits of experimental error. With levulose and insulin, on the other hand, the rise in the respiratory quotient is immediate and well-marked. This appears to indicate that levulose is more easily utilized by the diabetic organism than glucose and may be the explanation why levulose is so inefficient in controlling hypoglycemia (80). Wilder and Boothby suggest that the effect of insulin is to convert carbohydrate into an easily oxidizable and polymerizable form and the ketose, levulose, is closer to this reactive form than is the aldose, glucose. The specific dynamic action of the two sugars is about the same with and without insulin; the levulose curve being the higher in both instances. No evidence of a permanent rise in the basal respiratory quotient was noted. The basal metabolism was also little changed.

Joslin, Gray and Root (71) report an average increase in basal metabolism of 9.4 per cent. Three out of eleven cases showed no increase—1 case showed 24 per cent increase—in basal metabolism. Using smaller doses of insulin than Wilder and his associates and administering a mixed meal of protein, fat and carbohydrate, Joslin found, in some instances, that the respiratory quotient rose to a

very moderate extent and, in another instance, when successive doses of insulin were used, from 0.81 to 1.02. There was a marked increase in the basal metabolism accompanying this rise in respiratory quotient. In one instance the ingestion of levulose alone caused a greater rise in respiratory quotient than when insulin was administered at the same time. The high respiratory quotient, however, persisted longer in the experiment in which insulin was used. The basal respiratory quotients before and after a period of insulin treatment show increases so small as to bring them within the limits of experimental error.

Fitz, Murphy and Grant (73) report the effect of insulin on the respiratory quotient in 4 cases of diabetes. In all of them the respiratory quotient was definitely increased. In two cases the respiratory quotient was still comparatively high on the third day following injection of the insulin. This suggests the possible storage of carbohydrate in a form utilizable by the body or a prolonged action of the insulin. After fourteen days without insulin the respiratory quotient returned to 0.73—level characterizing severe diabetes. Basal metabolism was not markedly affected except in one case where the total calories per hour rose from 32 to 41.

McCann, Hannon and Dodd (86), in several cases show the initial decrease in the respiratory quotient when glucose is administered after insulin, as previously shown by Wilder and associates. As insulin treatment progressed it is interesting to see this peculiar fall give place to a distinct rise in the respiratory quotient.

Kellaway and Hughes (56) have contributed observations on the effect of insulin upon the metabolism in a normal person. A medical graduate volunteered as the subject. Two experiments were carried out with ten and eight rabbit doses of insulin respectively. Definite increase in the respiratory quotient occurred coincidently with the fall in blood sugar, as had previously been found in diabetes. The observed increase in oxygen consumption affords definite evidence of increased combustion of glucose. The authors contend that the rise in the respiratory quotient is due in part, to transformation of glucose into some complex that is poor in oxygen. Though it is not unlikely that this is sometimes the case, calculations based on their data fail to lend support to the hypothesis.

Lyman, Nicholls and McCann (57) determined the respiratory quotient and heat production in 5 normal men and 7 diabetic patients before and after insulin administration. In all cases the respiratory quotient rose and the heat production increased. Epinephrin caused a rise in the respiratory quotient and heat production possibly because of overventilation. Administration of the two drugs simultaneously, or following each other, on the whole produced a less variation from the basal values for respiratory quotient and heat production than when either was administered alone. The alterations in the metabolism of diabetic subjects were not as marked as in normal men.

Davies, Lambie, Lyon, Meakins and Robson (87) found a decrease in the respiratory quotient after insulin administration in a patient with acidosis and suggested that the destruction of blood ketones leaves alkali free to combine with some of the carbon dioxide produced. In a second case the respiratory quotient rose decidedly following the injection of insulin. The bicarbonate reserve was, in this case, nearer the normal than in the previous instance.

Rabinowitch (88) has published a table showing the effect of sixteen units of insulin on the respiratory quotient, the sugar, acetone and CO_2 combining power of the blood, together with the titratable acid *plus* ammonia and the glucose of the urine collected at short intervals, in a severe case of diabetes with acidosis. The respiratory quotient rose steadily from 0.724 to 0.804, coincidently with a fall in sugar and acetone bodies and an increase in the CO_2 combining power of the blood. The excretion of sugar and acid decreased in the urine. Since the respiratory quotients for diacetic acid and β-oxybutyric acid are 1 and 0.89 respectively, Rabinowitch is careful to point out that the observed rise in respiratory quotient may have been partly due to the combustion of the acetone bodies. He also groups diabetic patients according to their tolerance for total glucose (G), and shows that the basal respiratory quotient rises with increasing tolerance. In a diabetic, a tolerance of 75 grams G was increased by the administration of insulin to 125 to 150 grams G. The basal respiratory quotients during this period rose from 0.75 to 0.79, the latter corresponding to a tolerance of about 175 grams G. This difference has been interpreted as indicating storage of carbohydrate. Coincident

respiratory quotients and blood sugar curves after the administration of glucose with and without insulin have been interpreted in the same way. Even in normals we know so very little about the blood sugar curve after glucose ingestion, though much work has been done on it, that one would be very reluctant to subscribe to the interpretation unless supported by a very large number of observations.

Burgess, Campbell, Osman, Payne and Poulton (89) found that a severe diabetic under treatment for some months with insulin (75 units per day) showed a very high respiratory quotient—1.19, 1.08, 0.98 on three successive days. Twenty-three and a half hours after the last dose was given the respiratory quotient was 0.86 and 0.86, and the following day it was found to be 0.84. In 1 case 100 units of insulin were given in error, and it was necessary to give 110 grams of carbohydrate to counteract its effect. It was found that 50 grams more sugar should have been excreted than actually was the case. A storage of 50 + 110 = 160 grams of carbohydrate occurred under the influence of the insulin. On the third day the blood sugar rose, and 85 grams extra sugar were excreted. From these premises, they conclude that these 85 grams of carbohydrate have been stored in the tissues in some complex form and were then liberated as glucose. The remaining 75 grams of sugar they assume were burned.

On the whole, then, the evidence goes to show, in spite of the very evident difficulties of interpretation of the results and the comparative paucity of experimental data, that there is a rise in the respiratory quotient after the administration of insulin. There, further, seems to be a tendency for the high respiratory quotient to persist over several days, indicating either that the storage complex produced from carbohydrate by insulin requires no further insulin in its catabolism or that insulin has a more prolonged action than has previously been believed. That the result is not due to actual increase in the endogenous insulin production has not been satisfactorily shown, though this is most improbable. In several of the cases the insulin treatment was not sufficiently long to permit of such an improvement in the condition of the pancreas. Particularly in the severe cases with decidedly low basal metabolism, an increase in the latter occurs after insulin administration. Additional evidence is provided by

Wilder and Joslin and their associates that levulose is somewhat easier to metabolize than glucose. Even though the results lack the advantage of prolonged observation there is considerable evidence from the clinical course of diabetics under insulin that they are in the main correct. The explanation of the respiratory quotients exceeding one is still somewhat obscure. The simplest explanation is that carbohydrate is reduced to fat. There is no good reason to suppose that diabetics under insulin cannot convert carbohydrate to fat or, at least, into some other complex that is poor in oxygen. Observations on the metabolic rate and respiratory quotient occasionally bring to light anomalous results which cannot as yet be satisfactorily explained, and it is better to reserve judgment until a larger amount of data has been accumulated.

GLYCOSURIA

Loss of glucose to the body is not the most serious defect in the metabolism of the diabetic patient. It is, however, a warning signal of the failure to metabolize sugar efficiently, and on this account is of importance. The original observations (30, 68) that sufficient insulin would control glycosuria in all cases of true diabetes mellitus has been substantiated by every writer who has used it intelligently—so many now as to preclude the possibility of mentioning them. In approximately 600 cases of diabetes under treatment in Toronto insulin has not failed. Further, as Woodyatt (46) pointed out, a test with insulin is of value in the differential diagnosis of the glycosurias—diabetic, true renal and otherwise.

Insulin will increase carbohydrate utilization whether glycosuria is present or not and this has led some to ignore the well known fact that the diabetic showing glycosuria steadily and surely decreases in tolerance for carbohydrate. The other beneficial effects of the use of insulin, such as increased strength and vigor, brighter mentality, increase in weight, etc., may all be present but it surely cannot be satisfactory treatment not to give every chance to permit the patient's remaining tolerance to increase. Nor is it true that it can be *satisfactorily* replaced with insulin. Insulin is a crutch which slips at

times. The larger the dose the greater the danger of hypoglycemia and the greater the difficulty of adjusting suitable dosage.

Admittedly, when insulin was first employed it was somewhat difficult to keep the patient aglycosuric. There was, therefore, some justification for those who, rather than risk hypoglycemia with preparations of insulin which varied exceedingly in potency, were content to obtain the other benefits of the drug for their patient. We hold the position, however, that glycosuria in diabetes is a failure in treatment and so have consistently endeavoured to avoid it with rather remarkable success from the outset. Frequent repeated blood sugar examinations have enabled us to test the comparative efficiency of a particular batch of insulin on a well stabilized patient and to judge of its relative efficiency for other patients. For smaller clinics or for individual patients this would have been impossible but today the preparations are so well standardized that hypoglycemia from this cause does not occur.

Wilder (45) and his associates designedly permitted glycosuria for the reason given above. Woodyatt has found it possible to keep his patients sugar-free in most cases. "Old cases with low fixed tolerance limits have been difficult to keep sugar free . . . . and it would not seem necessary that they do so, since they have no natural tolerance to lose." With the first phrase the writer would agree and, if it be true that they have no natural tolerance, would agree also to the latter part. Cases without tolerance are comparatively few in number and very difficult to treat.

Geyelin (74), working with children and encountering the special difficulties of feeding and caring for these little patients regarded it as safer to permit glycosuria than to risk hypoglycemia. With the present more accurate assay of insulin he has lately adopted a policy of keeping the patient aglycosuric (personal communication).

Fitz, Murphy and Grant (73) report patients made sugar-free with insulin but give no indication of their general policy.

Allen (75) consistently endeavours to prevent glycosuria in his diabetic patients, whether under insulin treatment or not, and Joslin (81) specifically states, "A sugar free urine is just as necessary, in my opinion, with diabetics treated with insulin as diabetic cases treated

without insulin. I believe that, unless the urine is kept sugar free during the additional length of life these patients will enjoy, complications due to hyperglycemia and glycosuria will ensue."

HYPERGLYCEMIA

The maintenance of normal blood sugar levels is not so easy in severe diabetics under insulin treatment as it is in the under-nutrition types of treatment, since the immediate, or blood sugar lowering, effect of insulin is of comparatively short duration and repeated injections must be used to accomplish this object. Fortunately it seems to become easier as the state of nutrition of the patient is improved and the tendency to hypoglycemia becomes less, possibly because of the increased glycogen content of the liver and muscle tissues. Campbell and Fletcher (80) observed in such patients, as well as in normals and non-diabetics, that a suitable dose of insulin would lower the blood sugar to the normal level for many hours without the occurrence of hypoglycemia. This is more difficult to accomplish in the emaciated subject and also in the patient who has an extremely low tolerance for total glucose. In certain of these cases hypoglycemia is very readily produced by small doses of insulin. Caution must be observed in commencing treatment in such cases.

Fortunately, even these cases are likely to have a high blood sugar and consequently a large amount of carbohydrate stored in the tissues as glucose, unless partial starvation has been invoked as a preliminary to insulin treatment. One can usually depend upon the tissue sugar to guard the patient against hypoglycemia. The dose of insulin used for freeing the urine of sugar must, however, be promptly reduced if it rapidly becomes sugar free. In order to determine this, as well as the proper spacing of the dose, patients should have the urine collected at short intervals and tested for sugar, at least during the first forty-eight hours after starting insulin treatment.

These difficulties plus the additional expense and inconvenience of having blood sugar tests made have induced many to question the necessity of maintaining normal blood sugars in treating these severe cases. Those whose convictions permit glycosuria in the diabetic naturally have no trouble over this refinement of diabetic treatment.

To those who feel that it has been satisfactorily demonstrated that the aglycosuric diabetic lives longer and more comfortably than if glycosuria is permitted, the question of permitting hyperglycemia is a very important one. The Rev. Mr. X acquired diabetes at twenty-eight, with typical acute onset. He lived thirty-two years without treatment and was not known to be sugar free for any time. A good many patients who knew him have not lived nearly so long. When I was called to see him he had gangrene of the anterior half of the right foot with a spreading infection in the leg. No pulsation could be felt in the sclerosed vessels below the femoral artery on the left side. He was drowsy; breathing was a labor; and he was very weary. His temperature was 102°F. He died more of infection perhaps than of the diabetic coma which supervened. But, in the previous years, was he comfortable? For twelve years he had suffered from cramps in the legs on moving about. He was ataxic; he was uncertain of the position of his feet; later he could not write because of cramps in the hands. His eyesight partially failed him. He lost flesh. Intermittent polyuria became continuous and coupled with enlarged prostate, incontinence developed. He himself noticed his growing irritability and the development of an aphasia and realized its import.

Many times a similar picture develops more rapidly. We know that in the normal person glycosuria does not occur and, further, that the blood sugar is never raised to any great degree even after the ingestion of large amounts of glucose. If insulin is used only to keep patients alive shall we in the future see more of these cases with marked degenerative phenomena? Not from the glycosuria surely, but hyperglycemia is the only other related symptom. If it be true, and it must be remembered that it is not yet proved, that hyperglycemia predisposes to sclerosis of vessels and other degenerative phenomena, then sufficient insulin, endogenously produced or artificially administered, to keep the blood sugar normal is essential in treatment. But, further, we do know that glycosuria in the average case of diabetes is inimical to his best interests and that his tolerance for carbohydrate is more or less rapidly destroyed thereby. Consideration makes it apparent that it is not glycosuria, *per se* which produces this effect but excessive stimulation of the pancreas by the accompanying hyper-

glycemia, and it has been considered the best practice to remove this by diets below the tolerance of the patients. Those whose blood sugar could not be lowered by diet often broke to a lower level of tolerance. The pancreas of the aglycosuric diabetic who is allowed to have hyperglycemia is subject to the same overwork and resultant damage as the pancreas of the untreated patient. The results are possibly more gradual but there is no doubt as to the progressiveness of the condition.

PROTEIN SPARING ACTION OF CARBOHYDRATE

In a number of the cases reported by Banting, Campbell and Fletcher (69) the protein sparing action of glucose is demonstrated. Similar results have also been obtained by Wilder (45) and by Fitz, Murphy and Grant (73). Some of Allen's protocols (75) also illustrate this action. To show this action, all of these observers have depended upon the variations in output of urinary nitrogen in severe diabetics, with and without insulin. More complete metabolism experiments with analyzed diets are highly desirable since there are several objections to this method with the type of diet commonly used by the diabetic patient. It is probable, however, from some preliminary observations that such a study will only increase the already striking evidence of the preferential utilization of carbohydrate over protein when sufficient insulin is available to burn the former. On the reduced diets commonly used in diabetic treatment this protein sparing action is of some considerable importance, since upon it depend the possibilities of the emaciated patient regaining necessary weight and strength, as well as restoring the functional efficiency of organs severely under-nourished. The mere increase in weight of a patient, which may be brought about by retention of fat, salt and water, can have but a limited beneficial effect, and that mostly psychic in nature. The restoration of muscle and organ mass by actual increase in the total body protein is much more important for the continued well-being of the patient. The fact that such protein sparing action can be demonstrated on dietary protein allowances of $\frac{2}{3}$ gram of protein per kilogram body weight, as shown by Wilder (45) and ourselves (69), is an indication of the adequacy of such amounts of protein for the needs of the body.

LIPEMIA

Considerable theoretical interest is attached to the behavior of the blood fats under insulin treatment, but as yet they have been rather imperfectly studied in man. Quite early it was noted (30) that visible lipemia disappeared under treatment. Actual figures were not published but it did not appear more striking than one often observes on dietetic treatment alone. Davies, Lambie, Lyon, Meakins and Robson (87), in a preliminary communication, note qualitatively the disappearance of visible lipemia in 2 cases. Wilder and his associates (45) report analyses of blood fat in 3 cases without significant alterations. Joslin, Gray and Root (71) also report analyses showing a slow decrease in the blood fats. Considerable quantities of excess fat may be present in the serum without producing a visible lipemia. In our experience the total blood fats under insulin treatment tend to fall rather slowly. No definite relationship to insulin administered or increased carbohydrate metabolism has been made out. The disappearance of lipemia is certainly more rapid in those cases where no fat is being fed to the patient and acidosis is rapidly abolished. Hardy (103) has reported disappearance of lipemia retinalis under insulin treatment. Major (104) has shown that in two cases the eruption of diabetics due to deposition of cholesterin crystals and known as Xanthoma diabeticorum disappears after treatment of the patient with insulin. He believes that the clearing up of the lesions is due to good blood supply and to disappearance of lipemia and hyper-cholesterinemia.

LUXURY USE OF INSULIN

The so-called "luxury use" of insulin was a matter of some concern during the earlier period of treatment with the drug, while supplies were still relatively scarce. At that time it was considered justifiable to place a limit upon the amount of insulin obtainable by any patient in order that others should not suffer. The large supply of insulin now available has brought about its use by many physicians who, being more or less unfamiliar with the clinical course of diabetes, are using it unnecessarily (luxury use). The use of insulin and precari-

ously high diets to fatten a diabetic unduly, or to satisfy a gluttonous appetite, or to avoid the necessity of dieting reveals a lack of intelligent foresight on the part of the physician as well as a lack of resourcefulness in the treatment of his patients. For the patient himself there is increased danger of acidosis, with the constant risk of an incorrect balancing of the diet in relationship to insulin, so that either hypoglycemia or hyperglycemia and glycosuria are often present, resulting in decreased tolerance and degenerative phenomena associated with diabetes of long duration.

Several writers (81, 105, 106) have emphasized the danger of acidosis and coma resulting from the sudden discontinuance of insulin treatment. The result is not of course comparable with the prohibition of narcotics to the drug addict but is analogous to the results of sudden decrease of tolerance for carbohydrate in diabetic patients who acquire acute infections. Wilder mentions a patient who died consequent upon being without insulin for 36 hours. All patients should be warned of this danger which is the greater the more liberal the diet and the higher the dosage of insulin ordered. The danger is probably increased by any exertion or by an artificially induced or artificially maintained state of hypernutrition of the individual. Were the so-called "cures" (temporary overfeeding of mild diabetics with accompanying insulin administration) now being attempted in Europe and elsewhere not unsound on other grounds this risk should act as a deterrent. Bed rest, increased fluid intake and immediate reduction in diet, particularly the fat, should be enjoined on a patient compelled to forgo insulin temporarily for any reason.

POLYURIA

The increased amount of urine secreted by patients suffering from diabetes mellitus has usually been thought to be due to the diuretic effect of the sugar excreted along with it. Three factors—increased volume, sugar content, and high specific gravity—are commonly associated. Frequently a necessary uranalysis has been neglected because of a report of the excretion of a normal daily volume of urine. The fact is: the percentage of sugar in the urine may vary quite independently of the volume or the specific gravity and, further, on account

of the variations in the amount of inorganic salts and other organic substances in the urine there is no way of even roughly approximating the urinary glucose output by the specific gravity or by any of the qualitative tests. In the majority of patients with diabetes amenable to dietetic measures there is marked reduction in the excessive thirst and polyuria when the patient becomes aglycosuric.

An unbroken night's rest and increased comfort during the day, when polyuria was reduced, have often induced a discouraged patient to persevere with dietetic treatment. All patients heretofore made sugar free by dietetic means did not receive an equal degree of relief from the polyuria and this lack of relief was ascribed to the diuretic action of the hyperglycemia, though other patients with fully as high blood sugar levels early became free from polyuria. The advent of insulin has not changed this situation. Some patients who could not be made aglycosuric without insulin show a decreased urinary output when the glycosuria is prevented by the use of insulin. Some eight of our patients receiving insulin treatment, nearly all cases of the most severe type, continue to have polyuria in spite of becoming aglycosuric and having a normal blood sugar level. Polyuria in these cases appears to be an obligatory condition unrelated to diet or to renal disease. It is interesting to note that pituitary extract to some extent controls the polyuria, though it would be premature at present to postulate a combined pancreatic and pituitary lesion without further study of the condition. The power of the kidney to concentrate the urine is not lost in these cases since the specific gravity promptly increases under the influence of pituitary extract.

DURATION OF TREATMENT

Evidence related to the time a diabetic is under treatment with insulin must be added to the above mentioned immediate effect. It is conceivable that a patient might show temporary improvement without permanent benefit from insulin or from any other type of treatment. Incidentally, it may be pointed out that the benefits derived from prolonged treatment with insulin furnish a further argument that it is the necessary hormone that is lacking in the diabetic organism.

Three years of treatment of severe diabetic patients with insulin, resulting in marked improvement in the physical condition of the patients and their ability to do work, together with a lack of any evidence of deleterious effects, is sufficient guarantee that insulin can be continuously used without its value becoming impaired by unforeseen occurrences. Under older methods of treatment these patients, or at least a large proportion of them, would now be dead. It is common experience that life expectancy in severe diabetes has been prolonged. The types of dietetic treatment employed by various clinicians have been so diverse that the use of insulin in treatment appears to be the only additional common factor to which the increased duration of life can be related.

The amount of food consumed by the diabetic patient under insulin treatment has been far in excess of his previous tolerance. The assimilation of these foods without glycosuria or acetonuria makes it apparent that they must have been stored or metabolized. The former possibility is ruled out by the fact that the body weight does not become excessively raised, which would be the case if storage were solely concerned. Catabolism, of the foodstuffs, leading to greater energy output, accounts for the additional activities voluntarily undertaken by the patients. Since, previous to the use of insulin, all cases of severe diabetes were metabolizing high proportions of fat relatively to carbohydrate and, in most instances, were showing acetonuria, it follows that all the increased food assimilated as a result of insulin is not converted into fat and burned as such. If this were not the case the already excessive proportion of fat to carbohydrate metabolized would be increased and pronounced acidosis would certainly have resulted. Absence of acetonuria removes this possibility and makes it certain that sufficient additional carbohydrate has been burned to establish a safe ketogenic antiketogenic ratio.

CHAPTER X

Hypoglycemia

Although insulin possesses so many beneficent properties for the sufferer from diabetes mellitus it is not without drawbacks and contraindications. Some of these have been touched upon in the preceding pages. Indeed, its specific properties of influencing carbohydrate combustion, if used to excess, cannot fail to affect the well-being of the patient. It is important to remember that with insulin we are dealing with a most powerful drug, many times as toxic as strychnine. Its toxic action arises from the fact that, when present in excess, it inhibits the utilization of, or fixes in an unavailable form, the soluble carbohydrate of the body. This suggested the possibility that the body tissues might not only be deprived of sufficient food, but also that an acidosis might be produced from the attempt to utilize fat in the absence of the carbohydrate. Certain preliminary observations by Collip, in which he stated that insulin causes ketonuria in normal rabbits, seemed to support this view, but the well-known susceptibility of rabbits to changes in food supply renders the result somewhat doubtful.

The writer has seen three deaths from hypoglycemia on undernutrition diets, and Joslin also has reported four cases treated by dietetic methods. Woodyatt and Williams have also noted similar cases, and it is quite probable that there have been many other cases.

As noted above, we early became aware from the animal experiments that a condition of hypoglycemia would result from overdosage of insulin. The clinical state of these animals was carefully studied and reported as far as possible, and fortunately before any human cases were encountered the more marked stages of the condition were known and the treatment by carbohydrate and by adrenalin were tested out and found to be effective. A review of this work by Professor Macleod appears in Physiological Reviews.

Investigation on animals naturally fell short of giving a complete picture of the symptoms accompanying hypoglycemia, since subjective symptoms were not available for study. A report of the general features of this condition was made in the British Medical Journal, January 6, 1923, and the subject was more completely discussed by Fletcher and Campbell (70) in the Journal of Metabolic Research, November-December number, 1922, and additional studies reported at the meeting of the Society for Clinical Investigation, May, 1923. (Cf. Proceedings Society for Clinical Investigation, Abstract Journal American Medical Association, lxxx, 1641.)

The grave danger to patients from an unnoticed or untreated hypoglycemic reaction makes it important that every patient should be thoroughly familiar with it. With each bottle of insulin an instruction sheet is sent out giving this information as well as pointing out the cure. The warning cannot be too earnestly repeated; and in our clinic it has been the practice to induce an hypoglycemic reaction in patients about to be discharged and who may not previously have experienced one during treatment. In such cases, of course, there is no necessity for pushing the reaction very far. The patient should experience the early signs and symptoms up to the sweating stage, and also be instructed as to the cure of the condition. This precaution has been considered unnecessary in other clinics and, though we felt justified in maintaining it while the assay of insulin was uncertain, the number of reactions encountered decreased decidedly with the improvements in the assay. Recently we have been criticized for over-estimating the dangers of insulin but remain unrepentant. Aside from the fact that the earlier samples of insulin resulted in many more reactions than are found at the present time, apart from those produced for experimental purposes, insulin still causes death as the penalty for unsuitable dosage. Whenever its safety rather than its dangers becomes unduly emphasized we may be prepared for a considerable crop of "accidents." We are grateful for the support of practically all the foremost investigators who have each taken occasion to warn against the dangers of the treatment. This in no way lowers their opinion of its benefits when it is employed with suitable precau-

tions. As Joslin has phrased it, "Insulin is a remedy primarily for the wise and not for the foolish, be they patients or doctors."

Two deaths from insulin hypoglycemia have been seen. The first, an habitual drunkard, who had been refused insulin treatment at Toronto General Hospital because of this danger, received insulin from another clinic. Having been slightly inebriated, he arose in the morning with a distaste for food and omitted breakfast but injected thirty units of insulin subcutaneously. He transacted considerable business, walked considerably, hurried all morning in order to catch a train at midday. About noon he was brought as an emergency case to the Toronto General Hospital, having collapsed on the street. He was cyanosed; his heart was dilated; the heart sounds were weak; his breathing was difficult; he had edema of the lungs. Stimulants were given but he died before a needle could be boiled to administer glucose intravenously. The other case, from our own clinic, was a severe diabetic using forty units of insulin per day, who suffered from a gastrointestinal upset with vomiting. Without notifying his physician he took ten units of insulin without any food. Noticing the onset of the hypoglycemic reaction he ate an orange and, later, telephoned to his physician. Feeling improved he neglected to carry out the instructions given him to rest and take more glucose. A sudden collapse occurred followed by death before assistance arrived.

The symptoms and signs of the hypoglycemic state are more or less related to the level of blood sugar attained and become progressively worse as the blood sugar falls. In nearly all cases the blood sugar is below the normal level before the patient notices the abnormal symptoms. Occasional instances have occurred when symptoms that simulate those due to hypoglycemia have been described while the patient's blood sugar level was still above 0.1 per cent (0.110 and 0.130 per cent). These have also been noted by others who have used insulin in treating their cases. It is possible that they may be explained as protein sensitization reactions but this is not certain. They apparently occur in patients whose blood sugar level is permanently above normal and who have high thresholds of excretion for sugar. This type of symptom is deserving of further study since the speed of change

of the blood sugar level may be in some way the responsible factor, or it may be that hyperglycemia, in cases showing the symptom, is a necessary condition for the welfare of the individual, just as many arteriosclerotic patients feel better when their blood pressure is not lowered by means of drugs below a certain level.

The blood sugar level at which symptoms usually appear is about 0.08 per cent. It is known, however, that blood sugar percentages of 0.08 and even 0.06 per cent are many times encountered in normal persons who have not been treated with insulin without the characteristic symptoms of hypoglycemia. Also reactions which occur long after the insulin has been given are much less acute, other things being equal, than those which occur earlier. In such cases few symptoms may occur although the blood sugar is very low, and then suddenly disorientation, confusion, and even unconsciousness supervene. It may possibly be that it is the rate of lowering of the blood sugar—the dynamic factor—rather than the level attained that is responsible for the differences. Accidentally in one most remarkable case a blood sugar of 0.032 per cent was found. The patient presented no symptoms or signs of reaction and he had been given his evening meal before the result of the blood sugar test was known. Less marked degrees of hypoglycemia without symptoms have been observed on a number of occasions. The lowest blood sugar we have noted is 0.025 per cent. With the administration of glucose this patient recovered.

There is, then, no absolute blood sugar level at which certain signs or symptoms invariably occur. Occasionally a symptom from the severe class appears at a high blood sugar level. Nevertheless in most cases one can predict the blood sugar level from the severity of the associated symptoms.

The earliest symptom which most patients describe is a vague, indefinite feeling of uneasiness, an uncomfortable sense of impending danger. A peculiar mask-like immobility of the face with dilation of the pupils is often seen. Marked hunger may be complained of. Increase in pulse rate, with weakness, pallor, flushing, nervousness and tremulousness are early evidence of hypoglycemia. The blood sugar at this time is usually between 0.08 and 0.07 per cent. With lowering of the blood sugar to 0.07 to 0.055 per cent nervousness gives

place to anxiety and faintness; excitement and emotional disturbances with occasionally vertigo may occur. The physical signs at this stage include sweating, often most profuse, diplopia and incoördination. Marked excitement, emotional instability, sensory and motor aphasia, delirium, disorientation, delusions, confusion and bradycardia occur with blood sugar levels of 0.055 to 0.040 per cent.

With lower blood sugar levels the blood pressure may fall. Usually, however, it is well sustained. Unconsciousness has not been observed to occur until the blood sugar has reached 0.035 per cent. It may be accompanied by hypotonicity or hypertonicity of muscles and either lost or increased reflexes. Tremor, hypertonia, individual muscle twitchings and marked mental irritability mark the recovery from unconsciousness. Convulsions in children have been reported by Geyelin (74) and by others. Up until two months ago they had not occurred in any of our patients. In this case the child had a few clonic twitchings, which had ceased before my arrival, being succeeded by unconsciousness. Glucose solution injected intravenously promptly removed the symptoms.

The direct cause of hypoglycemia is the administration of an excess of insulin relative to the carbohydrate then available. It may result from excessive amounts, or unsuitable frequency of dosage or unsuitable time of administration. Failure to absorb the carbohydrate of the diet because of vomiting, diarrhea, duodenal ulcer, pylorospasm, etc., may render an otherwise suitable dose of insulin excessive in amount. Over-exercise may deplete the carbohydrate stores of the body or cause the endogenous production of insulin to become increased and so render the dose excessive.

Treatment of the condition consists in increasing the amount of circulating glucose in the body. Noble and Macleod (90) have shown that, injected subcutaneously, glucose is the only satisfactory antidote for the condition in rabbits. In man, when administered by mouth, a more extensive list of substances are suitable. With the exception of maltose, which is nearly as efficient, Campbell and Fletcher (80) have found the most satisfactory restorative is glucose. Substances other than glucose probably act in accordance with the ease with which glucose can be obtained from them. The order of

efficiency is: glucose, maltose, galactose, lactose, sucrose, levulose and glycerine. Starches are more slowly effective. Wilder (45) and his associates have confirmed the observation (68) that epinephrin may be used to combat insulin hypoglycemia in man and also the relatively short duration of its effect, and emphasized the necessity of administering carbohydrate immediately after the patient is able to swallow. Burn (48) states that pituitrin is effective in animals. For several months we have considered it inadvisable to recommend these drugs for clinical use in hypoglycemia. They are needed only during the unconscious state. The objections are both theoretical and practical but, in our experience, are not based on any deleterious effects attributable to the epinephrin itself. Certain cases, however, fail to show improvement with epinephrin because this substance acts by liberating glucose from the glycogen stores. Since these stores are much depleted in emaciated patients and may be very low after exercise the amount of glucose set free by epinephrin may be too small to relieve the hypoglycemia. At the same time it must be remembered that the work of the heart is interfered with by lack of available glucose. Since epinephrin increases the heart work the result might be most serious if no glycogen stores are available. Lyman, Nicholls and McCann (57) report 2 cases in which epinephrin failed to increase the blood sugar during insulin hypoglycemia.

The quantity of glucose necessary to restore the patient varies with the severity of the condition, that is: it is related to the degree of hypoglycemia present. Hence, the importance of determining by the clinical evidence presented the approximate blood sugar level. Though it will probably do little real harm it is better practice to avoid excessive sugar intake and the resulting glycosuria. The presence of glycosuria may make it difficult to interpret the clinical chart for two or three days and this symptom should be avoided if speedy treatment is desirable. If the premonitory symptoms of hypoglycemia are noted half to one orange will usually be effective. If the sweating stage is reached (blood sugar 0.07 to 0.055 per cent) the carbohydrate in an orange is insufficient unless a meal is imminent. A level tablespoonful of corn syrup is usually effective but should be repeated if relief is not experienced within ten minutes or if the patient recovers

only temporarily. More severe cases should have three or more tablespoonsful of corn syrup, or its equivalent, administered by mouth at once.[1] Patients who are unconscious should be given an intravenous injection of glucose solution. Fifty grams or more of pure glucose may be necessary in these cases. Every insulin patient should be given ample opportunity to realize his danger from the unintelligent use of this drug.

[1] In the severe stages glucose chewing candies are not recommended because of the danger of choking.

CHAPTER XI

Simple Ketosis, Acidosis and Coma

For our present views on these subjects we are largely indebted to the papers of Woodyatt (91), of Shaffer (92) and of Wilder (93). Limitation of space prevents discussion here of some of the most important phases of intermediary metabolism most clearly set forth by these writers. It may be taken, however, that a definite maximal amount of fatty acid may be completely oxidized without acetone bodies (at least of any moment) being produced when a certain amount of glucose is being burned. This glucose (G of Woodyatt) may be derived from the carbohydrate in the food, from 58 per cent of the body protein and from 10 per cent of fat, since it is known that glycerine (10 per cent by weight of the fat) can produce an equal weight of glucose. The writer does not intend here to go into the question as to the absolute accuracy of the figures. The significant point is that they form the basis of a most successful method of treatment for diabetes.

Marked increase in the ratio of fat to glucose undergoing metabolism will cause the production of the acetone bodies—acetone, acetoacetic acid and β oxybutyric acid. In small amounts these substances may appear in the blood and urine without causing abnormal physical signs or symptoms. This condition may be called simple ketosis. With increased over-production, or delayed elimination of the acetone bodies, however, physical signs appear, due partly to disturbances in the hydrogen ion concentration of the blood and partly to the toxic action of these substances. Milder degrees of this toxic action constitute a state of acidosis but severe degrees, due to an increased amount or a prolonged action of these substances in the body, result in diabetic coma. With these symptoms are associated alterations in the mineral and water balance of the blood and tissues, and in all probability changes in the physical and chemical state of the

body proteins. In cases in which severe acidosis and coma occur there is evidence of dehydration. Many times acidosis is due to a temporary lowering of tolerance resultant on an acute infection. In the severe stages it seems probable that the pancreatic damage is so severe that the islet cells have ceased to function. In the first patients treated with the pancreatic extracts (30) an immediate reduction in the ketonuria occurred and encouraged the belief that acidosis and coma might be efficiently treated by their use. It later was found (34, 68) that not only ketonuria and ketonaemia could be made to disappear but also that the CO_2 combining power and alveolar CO_2 tension of the blood return to normal levels when insulin is used. Coincidently with these effects the patients were relieved of the symptoms of acidosis and coma from which they were suffering. Nearly all our collaborators have taken occasion to confirm these results and there are now on record numerous tables illustrating these effects of insulin. More recently Cullen and Jonas (94) have demonstrated exceedingly low hydrogen ion concentrations in the blood of diabetic coma cases with subsequent return to normal values under insulin treatment.

The amount of insulin necessary to control acidosis varies considerably. It is well known that dietetic treatment will control the condition in some cases, and patients showing simple ketosis without clinical symptoms may usually be relieved by this means. The more severe degrees of ketosis may require insulin. Many patients exhibiting the severer degrees of ketosis would undoubtedly recover on suitable dietetic treatment, rest, warmth, etc., but when definite clinical symptoms are present it is preferable to use insulin than to risk the occurrence of coma. With the exception of cases of acidosis occurring during infections an initial dose of forty units of insulin and twenty units every four hours for six doses will be ample to control the situation. Most cases will require much less. The required dose of insulin to control acidosis during infections is much more difficult to approximate. The tolerance of insulin in this condition is enormous but the patient must be closely watched. In all cases carbohydrate should be supplied in amounts sufficient to prevent hypoglycemia, and the urine repeatedly tested for sugar. Suitable diet should be given

as soon as the patient will take it and the insulin reduced gradually. Thirty to forty units should be given daily for two or three days until the danger of relapse is over. It is desirable also to observe the alveolar CO_2 tension, CO_2 combining power of the plasma and the blood sugar, but most cases can be successfully treated with urinary examinations for glucose and diacetic acid alone. The prompt treatment of acidosis with insulin when first diagnosed should diminish the number of coma cases seen in the hospital. Cases of coma about to be transferred to the hospital should also receive, as soon as possible, fifty to sixty units of insulin with carbohydrates (by stomach tube if necessary).

There are very real benefits from dietetic treatment in cases of acidosis. We have not, however, cured diabetic coma by these means nor have we cured coma by the use of alkalies. The under-nutrition school regards it as impossible for coma to develop in patients on their type of treatment. Unfortunately this has not been our experience: on the contrary, even on starvation in cases without sufficient tolerance, coma may supervene. In this connection the experience of Fitz, Murphy and Grant (73) may be noted. Table VIII, page 764, in the Journal of Metabolic Research, volume ii, records a case on treatment for five days by Joslin's method, followed by two days of fasting. The acidosis increased. Small doses of insulin plus a diet relatively high in fat and total calories improved the acidosis. Joslin's (95) case 2366 developed coma in the hospital and recovered under "starvation" treatment without insulin or alkalies. This fact, and the fact that 15 other patients with acidosis recovered, should not, however, be used to discredit either the insulin or alkali therapy of diabetic coma. In 1921, while visiting the Mayo Clinic the writer saw Wilder treat an advanced diabetic coma with alkali. Recovery ensued and the patient was living and doing well a few months ago. During a visit to Toronto in 1922 Wilder saw Fletcher treat a child of six years in very severe acidosis, though still able to be roused, with insulin. This patient also recovered. At the time the American manufacturers of insulin were encountering great difficulty in maintaining the potency of the drug and Wilder, along with many others, was somewhat skeptical of its value. He expressed himself as satis-

fied that insulin was the effective agent in this case. The patient is still progressing favorably on dietetic treatment with insulin. None of these physicians however, failed to use other means of treatment. The other measures—rest, warmth, fluids,[1] enemata and supportive measure applied to the circulation—are not needless; they are valuable adjuncts in treatment. It is the verdict of many investigators that the statement "Insulin is a specific in the treatment of diabetic coma" still stands, but today one would not care to treat coma by means of insulin alone.

With regard to the dose of insulin in coma and its administration, there is still a difference of opinion. The majority of investigators, including Joslin and Wilder, are in favor of small dosage. With the wide circulation of Joslin's (96) paper advising ten units of insulin as an initial dose in coma cases and the emphasis that has been placed on the dangers which may attend the treatment, 2 cases in one town, treated by a local practitioner, received five units of insulin each. Needless to say they died. Apparently Joslin has more recently changed his policy (95) and in case 3382 he gave forty units immediately, that is, four times as much as he previously recommended as an initial dose. This was followed by further injections so that one hundred units are given in six hours. We often give one hundred units immediately. Allen (75) and Woodyatt (46) use smaller initial doses (sixty to eighty units). We have not observed any deleterious effects from such large doses provided measures are taken to prevent hypoglycemia. For this purpose it has been the custom in Toronto to use 1 gram of glucose or other carbohydrate for each unit of insulin. Joslin regards this as excessively high, pointing out that a blood sugar of 0.5 per cent means 15 to 25 grams of sugar in the blood and that there may be other carbohydrate stores such as glycogen and protein. It is, of course, unnecessary to state that blood sugar is not always

[1] The influence of the dehydration factor in many of these cases is but little less important than the acidosis itself and its treatment by liberal fluid administration must not be neglected. Cases of coma due to dehydration alone, though fortunately rather uncommon, do occur. Much more commonly dehydration is present, often unnoticed, in various febrile diseases, conditions associated with vomiting and intense diarrhea, the thyrotoxic crises and particularly in prolonged diabetic acidosis when the blunting of the sensation of thirst together with polyuria may give rise to a remarkable loss of body fluid.

0.5 per cent in coma and, indeed, may be normal. Further, it is not known that the glycogen stores use further insulin for their metabolism. The depancreatized dog may not develop a high DN ratio and low respiratory quotient and glycogen may still be present in the liver for three days. The glycogen stores in the human diabetic in coma, in any event, must be rather small. The protein breakdown is small in amount and but little insulin will be used for metabolizing carbohydrate from this source. Moreover, glucose derived from this source is not so efficient an antiketogenic agent as that derived from carbohydrate itself. These imaginary safeguards should not, therefore, be relied upon to save a patient from an hypoglycemic death. The safest practice is that a retention catheter should be placed in the bladder and the urine tested hourly for glucose and if this becomes low in amount more glucose should be administered immediately. But, further, it is well known that carbohydrate is burned in preference to fat and protein. By supplying this carbohydrate along with sufficient insulin to metabolize it no further breakdown of body fat or body protein is necessary to provide energy. Thus no further acetone bodies can be produced. The patient must then burn or excrete the stored ketones only in order to be relieved of his ketonic acidosis. Glucose is needed both to prevent hypoglycemia and to stop ketone production. The theoretical danger of damaging the pancreas through the production of hyperglycemia by administration of carbohydrate should not influence one for two reasons: the first being that the pancreas of a patient in coma is apparently inactive and the second that hyperglycemia is usually present in any event. It is interesting to note that Joslin (95) permits the latter as necessary to guard against death from hypoglycemia. In these views we have the support of Allen, who writes "This advice is practically identical with that already given by the Toronto investigators who are fully justified in their view that the harmfulness of carbohydrate excess for a day or two is negligible in an emergency of this kind" (75).

The first 15 coma patients treated in Toronto (30, 34) with insulin received no alkali. That the larger half of these cases recovered, sufficiently demonstrates the fact that insulin with other measures, as noted above, but without alkali, is effective in the treatment of

coma. It is felt, moreover, that the results would have been much better had severe infections, such as pyemia and pneumonia, been absent in several of the cases. During the investigation of these and other cases of acidosis (34), it was found that in some instances the ketones could be made to disappear from the blood and urine without a corresponding increase in the CO_2 combining power of the plasma. This was attributed to a deficiency of base or unusual combinations of the remaining bases of the blood and tissues. In a paper read in April, 1923, Fitz, Bock, Starr and Field (97) noted the same condition but attributed it to the effect of an hitherto unidentified organic acid. More detailed evidence in favor of this view has recently been furnished by Starr and Fitz (107).

There is no doubt that a majority of coma patients have their CO_2 combining power raised to the lower limits of normal (50 volumes per cent) by the combustion of the ketonic acids under the influence of carbohydrate and insulin. In such cases (which, by the way, cannot be distinguished from the others except by prolonged chemical investigation) the use of alkali will not be necessary except in so far as it may be of value in shortening the period of coma and the abnormal chemical states associated with it. That this is worth while the majority of investigators are prepared to accept. In the other cases who present a low CO_2 combining power after the ketonic acids are burned, the use of alkali is imperative.

Palmer and Van Slyke (98) have shown that the administration of 1 gram of soda bicarbonate per 84 pounds body weight raises the CO_2 combining power of the individual's blood one volume per cent. Since, in most cases, we will be dealing with a patient whose CO_2 combining power will rise to fifty volumes per cent with the katabolism of the ketone bodies, it seems safe to use 20 grams of soda bicarbonate per 84 pounds of body weight, thus raising his CO_2 combining power to seventy volumes per cent—a value still below the upper normal limit —and alkalosis will be avoided. In these cases some acceleration in the improvement of the patient may be expected. But in the occasional case the ketones are destroyed, and insufficient alkali is thereby released to raise the CO_2 combining power. If the CO_2 combining power rises but to twenty-five volumes per cent that patient will

probably still die of acidosis. In this instance the addition of twenty volumes per cent to the CO_2 combining power is a very decided factor in the relief of the patient. The amount of alkali necessary in the average case will be about 30 grams of sodium bicarbonate or its equivalent. Many other investigators have adopted a similar dosage of alkali. Should later determinations of the CO_2 combining power show insufficient alkali reserve more soda may be administered. The reaction of the urine should not be relied upon as a guide to alkali therapy in these cases. If the urine becomes alkaline the therapeutic dose may have been very markedly exceeded and the patient brought into danger by alkalosis.

With the use of alkali in any case, Joslin entirely disagrees, pointing out that 4 out of 5 cases do not need alkalies. Joslin's (95) question is "Do you think there is any case of diabetes whose tissues are so robbed of sodium, potassium, calcium and magnesium, and whose kidneys are so devoid of the power to form ammonia that one ounce of soda will save him?" But, why did the coma develop if these substances were present in the body and available to save him? The quantity of soda used is not material to the argument so long as it is the therapeutic dose. If, indeed, alkali will only help to save one out of five comas, surely a 20 per cent less mortality in diabetic coma is acceptable, and it is worth giving it to all 5 cases in order to save the one.

RÉSUMÉ OF TREATMENT

Patients showing ketone bodies in the urine, without clinical or other evidence of acidosis, may be placed on their basal requirement in calories as explained under dietary treatment, and their progress observed.

In a case of acidosis with clinical symptoms the required amount of insulin necessary varies considerably according to the severity of the case, the presence or absence of infection and dehydration, and the speed with which it seems desirable to improve the patient's condition. Forty units of insulin per day given in divided doses at six-hour intervals will hold a patient out of coma for days and the acidosis in the milder cases clears up as indeed will often occur on dietetic treatment

alone. Since only a limited amount of acetone bodies can be excreted per litre of urine, and the dehydration may sometimes be severe, it is advisable to provide the patient with large amounts of fluids ($\frac{1}{2}$ pint per hour at least) until symptoms disappear. Such patients should also go to bed, be kept warm and someone should be provided to nurse them. A saline or soapsuds enema is desirable and, in children, who are more liable to acidosis following a gastrointestinal upset than adults, often imperative. Inasmuch as I see no advantage in prolonging a case of acidosis and it can be emphatically stated that large doses of insulin do no harm when administered with sufficient carbohydrate to prevent hypoglycemia, I am in favor of liberal use of insulin: 40 units, first dose, with perhaps 20 units in four hours and repeated if necessary, will save much unnecessary suffering on the part of the patient and friends and unnecessary waste of the physician's time as well. It should be arranged that the patient receives 1 gram of sugar in some form per unit of insulin given. If frequent examinations of the urine for sugar are made there will be no danger of hypoglycemia. Since, by clinical signs and chemical tests alike, we are unable to determine the exact grade of severity of the acidosis in a particular case, all cases should be cleared up as promptly as possible. Diabetics with infection and acidosis should be regarded as being several times as severe as the evidence apparently warrants and suitable treatment for the infection, providing free drainage for pus, etc., should not be neglected. More and more the coma cases seen in hospital are patients suffering from inadequately treated acidosis with inadequately treated or fulminant infection. Dietetic treatment should be begun as soon as the patient is able to retain foods without distress. Soda is not usually required by the patient with acidosis though I believe a moderate dose, 10 grams, accelerates the recovery.

A diabetic patient in coma is an emergency. Careful diagnosis of the cause of the coma should not be neglected but time should not be lost in his treatment. Once, over the telephone, I advised insulin and glucose for a comatose known diabetic with marked glycosuria and a strong ferric chloride reaction in the urine. On arrival, the lack of acetone on the breath (which had been reported present), together with the type of breathing, led me to suspect an intracranial lesion. His

CO_2 combining power was found to be normal. The glucose administered prevented an hypoglycemia. Spasticity then paralysis developed. The patient died three days later with bilateral intraventricular hemorrhage confirmed by necropsy. I have been asked to bring insulin to another patient with cerebral hemorrhage and to three other patients suffering from uremia. In case a reasonable amount of evidence of diabetes was present, without evidence of other cause of coma, one is justified in giving the insulin and checking up the chemical findings as soon as the patient arrives in hospital. With the initial dose of insulin (40-60 units sub. cut.) glucose should be given by mouth. Transference to hospital in some cases may be difficult, if not impossible, and under such circumstances one must be content with improvised measures. Whenever it can be accomplished without excessive danger or fatigue to the patient it is worth the risk.

Patients arriving in hospital in diabetic coma who have not received treatment require larger doses of insulin. As speed is essential in the treatment of these cases and the rate of action of insulin is only doubled by taking ten times the dose, we commonly use 100 units of insulin intravenously as the initial dose. Most of the coma patients are dehydrated and fluid must be supplied liberally. Some of this may be given intravenously as 10 per cent glucose solution, at a rate not greater than 10 cc. per minute. If the pulse rises ten beats per minute discontinue the injection. Normal saline or 5 per cent glucose solution may be injected interstitially and given per rectum by the Murphy drip method after a cleansing enema has been given. Many patients difficult to rouse will respond by automatic swallowing movements when a teaspoonful of fluid is poured into the mouth. Except by direct injection into the circulation it is doubtful if too much fluid can ever be administered to a diabetic in coma.

Warmth must, of course, be provided. The room should be warm and warm blankets and hot water bottles used. Circulatory stimulation should be begun early, digitalis and coffee by mouth or per rectum being the most satisfactory stimulants, pituitrin and ether being used for more acute emergencies. In my opinion alkalies in moderate doses, 15 to 30 grams $NaHCO_3$, are of value when administered by mouth or per rectum in 5 per cent solution. The intravenous injection of sodium

bicarbonate solution is to be employed with caution as it may induce cardiac dilation and failure.

Hypoglycemia must be avoided and carbohydrate must be available to replace the defective fat metabolism as well as to burn up the ketones already produced. This is provided by giving the patient approximately 1 gram of sugar for each unit of insulin. The use of a retention catheter and testing of the urine for sugar each hour will give ample warning of a deficiency of available carbohydrate.

While many chemical methods ultimately yield interesting results the CO_2 combining power of the plasma with tests for sugar and diacetic acid in the blood and urine are the most useful. The clinical condition of the patient should be correlated with these if possible but cases may quite well be treated with clinical observation and uranalysis alone. Should the evidence available show improvement lesser quantities of insulin may be used subcutaneously and small quantities repeated until the patient is on a suitable diet with about 40 units of insulin per day and 40 grams glucose. The glucose is gradually reduced and smaller amounts of insulin given as required. Lack of improvement after three or four hours should indicate the necessity for further large doses of insulin and glucose intravenously.

CHAPTER XII

The Diagnosis of Diabetes Mellitus

The diagnosis of diabetes mellitus is usually easy when several of the classical signs or symptoms—hunger, thirst, polyuria, polyphagia, loss of weight and glycosuria—are present at the same time. Nevertheless, none of these signs and symptoms are diagnostic in themselves and without the symptom glycosuria being present when appropriate tests are applied, the other signs may safely be ascribed to some other disease. Glycosuria, itself, is not constantly present in diabetes of the milder grades, but when present becomes particularly significant when accompanied by ketonuria. The principal difficulties with diagnosis of diabetes mellitus arise from three sources: (1) Mistaken interpretation of the test for glycosuria; (2) presence of unusual or abnormal substances in the urine reacting like glucose; (3) the existence of glycosuria in conditions other than diabetes mellitus. The first difficulty often arises from inattention to the directions for use of the test solution or from the use of a test solution which reduces with other normal urinary constituents (uric acid, creatinin). Again, certain urines which have been allowed to become ammoniacal give no apparent reduction when sugar is present because the cuprous oxide is redissolved by the ammonia or ammonium salts present.

The most satisfactory course is to use one of the more recent sugar test solutions, such as Benedict's (for formula and directions see page 117), according to the method described by its author. If care is taken to avoid factitious reductions due to the use of chloroform or formalin as a preservative, a positive test with Benedict's solution can usually be relied upon as indicating the presence of an abnormal reducing substance in the urine. The urine should not contain more than a trace of albumin as otherwise, as when much phosphate is present, a greyish green turbidity which appears may lead to some confusion.

Dilution of the urine with an equal amount of water in such a case gives a negative test. If any doubt is present a fermentation test will usually establish whether or not a reducing agent in the urine is or is not glucose.

Unusual or abnormal substances such as lactose, glycuronates, pentoses, melanin, homogentisic acid, etc., are the cause of reduction of the copper salt by certain urines. They may often be differentiated by the history as in the case of lactose during pregnancy or the nursing period or by the use of the fermentation test. Glucose gives a positive fermentation test; the others do not.

Glycosuria may exist in two groups of conditions other than diabetes mellitus. In the first it is of a transient character, and in the second of a more permanent nature. A partial list of the first group of temporary glycosurics includes the anemias, toxic goiters, starvation, emotional stress, cerebral accident, such as hemorrhage, thrombosis or embolism, intracranial tumors, pituitary disease and concussion or fracture of the skull. A clinical history and physical examination of the patient will usually assist in differentiating these conditions from diabetes mellitus, but while valuable in the second group of cases, an extended study of the patient's response to dietary and other measures must be undertaken. This group which embraces the renal glycosuria of pregnancy, renal diabetes in chronic nephritis, idiopathic renal glycosuria, toxic renal glycosuria and certain cases intermediate between the renal type and true diabetes mellitus called diabetes innocens, have certain points differentiating them from diabetes mellitus and since their prognosis is good, should be carefully separated from the more serious disease. That they are not rare is evidenced by the fact that I have now collected a series of more than 40 cases, many of them being referred for insulin treatment because of failure to become aglycosuric on their original physician's treatment; others because of glycosuria without other symptoms found on life insurance examination, while a number were referred for investigation by their physician who found glycosuria while attending the patient for an unrelated illness. Certain characteristics assist in separating the group from diabetes mellitus. Apart from glycosuria they are symptomless and have all been discovered accidentally. The percentage of glucose in the urine

and the total daily excretion of glucose is never very high and is unaccompanied by ketone bodies, and, further, it does not increase proportionately with increased diet. No tendency to progress is to be noted even when on high allowances of carbohydrate. The respiratory quotient after glucose ingestion rises to one indicating carbohydrate combustion and it can be repeatedly demonstrated that glycosuria begins when the blood sugar is still much below the normal threshold of excretion for glucose.

Greater difficulties are presented by another group of cases showing septic infections, prolonged alcoholism, acute and chronic pancreatities, duodenal ulcer, gallstones and cholecystitis. Glycosuria, with or without other symptoms, often occurs in this group of cases and in part they progress into true diabetes mellitus. Probably they are best regarded as being temporarily diabetics and treated as such until the necessity disappears.

The attempt to separate a group of potential diabetics by means of the so-called "diabetic curve" in the blood sugar tolerance test has been of little value and so far as I am aware no potential diabetic in the literature has become truly diabetic. Certainly from among many hundred "diabetic curves" obtained in studying other diseases—arthritis, arteriosclerosis, goiter, etc.—there has come little confirmation of the theory. Blood relationship with a diabetic patient and obesity are far more closely related factors.

CHEMICAL METHODS OF EXAMINATION

For purposes of investigation of diabetes a large number of chemical methods are of value, though not absolutely necessary, in the treatment of a patient. As these methods in their most up-to-date form are available in texts on physiological chemistry, such as Hawk's, it seems unnecessary to burden this book with them. The qualitative and quantitative examination of the urine for sugar and the qualitative tests for ketone bodies in the urine are essential in the treatment of diabetes, while the estimation of the blood sugar from time to time is the only satisfactory laboratory index of the condition of the aglycosuric diabetic. Occasionally, in cases of acidosis and coma, an examination of the alkali reserve of the blood is of great value, but as it

requires somewhat more complicated apparatus and some technical skill and experience it will not be described here.

Collection of twenty-four hour specimen of urine

To collect the urine excreted during twenty-four hours void at a definite hour and discard the urine. All subsequent voidings up to and including that at the same hour twenty-four hours later are mixed, measured and a sample taken for the tests.

Qualitative examination for sugar

Benedict's Qualitative Reagent for Sugar:

Recrystallized copper sulphate	17.3	grams
Sodium or potassium citrate	173	grams
Sodium carbonate, anhydrous	100	grams
Distilled water to make	1000	cc.

Dissolve the citrate and carbonate in 700 cc. of water with heat. Filter if necessary and add the copper sulphate (dissolved in 100 cc. water) slowly with constant stirring. Cool and add water to 1000 cc. (This solution may be purchased prepared for use.)

Directions for use. To 5 cc. of Benedict's solution in a test tube add 8 drops of urine. Boil two minutes over a free flame or five minutes in a vessel filled with boiling water. Set aside to cool. If, after cooling, the mixture becomes absolutely opaque when shaken up, sugar is present. The color may be green, yellow or red, varying with the concentration of sugar present. With sugar free urine the test solution remains blue.

It may be suggested that the man who is regularly testing the urine may find it satisfactory to carry out the test in the morning while shaving. Wrench the thin blade from a pair of electric curling tongs partly immerse the round blade in the Benedict's solution, prepared as usual, and turn on the current for ten minutes; read the result immediately.

Quantitative examination for sugar

Benedict's Quantitative Reagent:

Pure crystallized copper sulphate	18 grams
Sodium carbonate, anhydrous	100 grams
or	
Sodium carbonate, crystalline salt	270 grams
Sodium or potassium citrate	200 grams
Potassium sulphocyanide	125 grams
or	
Sodium sulphocyanide	100 grams
Five per cent potassium ferrocyanide solution	10 cc.
Distilled water to make a total volume	1000 cc.

With the aid of heat dissolve the carbonate, citrate and sulphocyanide in approximately 600 cc. of water and filter if necessary. Dissolve the copper sulphate separately in about 100 cc. of water and pour quantitatively the solution into the other liquid, with constant stirring. Add the ferrocyanide solution, cool and dilute to exactly 1 liter. Of the various constituents the copper salt only need be weighed with exactness. Twenty-five cubic centimeters of the reagent are reduced by 50 mgm. (0.05 gram) of glucose.

Dilute the urine until about 25 cc. will be required to reduce the reagent (about 10 cc. to 100 unless the quantity is thought to be low). Take 25 cc. of Benedict's quantitative reagent, 25 cc. water, 5 grams Na_2CO_3 and bring to boil. Run in 18 to 20 cc. of diluted urine rapidly, but never allowing boiling to cease. Boil full *two minutes*. Now add urine in smaller amounts at a time, allowing full two minutes boiling between each addition. When the Benedict solution is near complete reduction it will show only a slight blue color. From this point onward the addition of the urine to the boiling Benedict solution must be cautious. The end point is marked by the disappearance of the blue color. Repeat the test using a more suitable dilution if less than 15 cc. or more than 40 cc. of diluted urine is required.

The percentage of glucose is determined from the equation:

$$\frac{5 \times \text{dilution}}{\text{volume used}}$$

and the number of grams of glucose by multiplying percentage by the volume and pointing off two places.

Diacetic acid

Gerhardt's test. To ¼ test tube full of urine add 10 per cent ferric chloride solution until the opacity produced just redissolves. If diacetic acid is present in any considerable amount the color of the mixture will become decidedly deeper brown than the ferric chloride solution. Confusion is sometimes caused by the use of aspirin and other coal tar drugs, headache remedies, etc., but the color produced by these drugs has a bluish or violet tint and does not disappear if the urine be previously boiled.

Rothera's test. Another method of examining for ketones which is perhaps somewhat too delicate for ordinary use is Rothera's test. It is sometimes useful for confirming the results of a ferric chloride test and may also be employed in detecting ketones in the blood plasma.

To 10 cc. add an excess of solid ammonium sulphate so that the urine is saturated. Then add a small crystal of sodium nitroprusside, followed by 1 to 2 cc. of strong ammonia. Mix and allow to stand for ten minutes. A "permanganate" color indicates the presence of acetoacetic acid. If the quantity is small the color may develop very slowly.

The fermentation test

In most instances a properly performed fermentation test will determine whether a reducing agent found in the urine is glucose or not. A fermentation test on urine should be accompanied by two controls: one made up with yeast and water to ascertain whether the yeast is producing gas; the other, with yeast and glucose solution (diluted corn syrup) to determine whether the yeast is active. One-sixteenth cake of fresh yeast is rubbed up with a portion of the urine and placed in the closed arm of the fermentation tube, all bubbles being carefully removed. After setting up the controls with water and glucose solution the tubes are set away in a warm place preferably in an incubator. If the controls show gas formation in the glucose tube only, examine the urine tube. Definite gas formation in an hour or two indicates glucose. On account of the fact that yeast carboxylase ferments urea

small bubbles of gas in the tube after twenty-four hours should be considered as negative evidence. Glucose, even in small quantities, produces much more gas in this time.

The estimation of blood sugar

The blood is usually obtained while the patient is fasting (before breakfast) and the examination should be proceeded with immediately, or some preservative used. The use of formalin, as recommended by Denis, has not proved satisfactory in my hands. The use of about 10 mgm. of one part thymol and nine parts sodium or potassium fluoride for each cubic centimeter of blood taken is a more certain anticoagulant and preservative. Blood so preserved may be allowed to stand for considerable periods before being examined by a laboratory.

Numerous methods of estimating the blood sugar have been proposed. Those using very small amounts of blood obtained from a finger prick are, as a rule, unsafe, unless one has gained special experience in their use. For most methods blood obtained from the arm vein with a small syringe and 22 gauge needles is the most satisfactory. Since the sugar content of plasma and corpuscles is nearly the same no significant error will be made by using whole blood for the test.

The normal values for blood sugar differ slightly with the methods used, but the normal range is 0.08 to 0.12 per cent.

While other methods have certain advantages for hospital work, the physician to whom a laboratory is not easily available requires a method which is relatively simple and, at the same time, fairly reliable. The Myers Bailey modification of the Lewis Benedict method is based on the reduction of yellow alkaline picrate solutions by glucose and heat to dark red colored solutions, probably containing picramates, and the estimation of the color produced by comparison with the color obtained from a known amount of glucose. The suitable quantity of blood (2 cc.) may be placed in 8 cc. saturated picric acid solution at the bedside and shaken, thus preventing destruction of the glucose in the blood; or a few milligrams of sodium oxalate may be added to the blood as an anticoagulant and the precipitation with picric acid completed within half an hour. Care should be taken that only a

carefully purified picric acid is used and that it, both as solid and in solution, is kept in a dark cupboard when not in use.

To the 10 cc. of blood-picric acid mixture in a test tube is added about 1 gram of solid picric acid and whole is ground together with a glass rod until the mixture assumes a light yellow color, when it may be filtered through a small filter or centrifuged. Three cubic centimeters of the filtrate or supernatant fluid is taken for analysis.

Preparation of standard stock solution

One gram of pure dry glucose is dissolved in saturated picric acid solution (1.2 per cent) and the mixture made up to 100 cc. with saturated picric acid solution and thoroughly mixed. This solution will keep for years if kept in a dark cupboard.

Standard solution

Two cubic centimeters of the stock solution are accurately measured into a 100 cc. flask and diluted to volume with saturated picric acid solution. Portions of this solution and the picric acid blood filtrate are now treated similarly.

Procure two or more test tubes graduated in cubic centimeters up to 25 cc., matched so that the distances between the 5 and 25 cc. marks does not differ by more than 1 mm. Into one tube put 3 cc. of the standard solution; into the other put 3 cc. of the blood filtrate. Add to each 1 cc. of saturated sodium carbonate solution; cap with tin foil or tea lead and boil in a beaker of boiling water fifteen minutes. Then cool by standing in a beaker of cold water three to five minutes. Dilute the standard solution to the 10 cc. mark with saturated picric acid solution. Similarly dilute the unknown blood sugar mixture until it matches color of the standard when mixed and observed against a white paper. The number of cubic centimeters of the diluted unknown divided by 100 gives the percentage of the blood sugar. When very high blood sugars are encountered it is advisable to dilute the blood filtrate with saturated picric acid solution and repeat the test. The method requires no expensive apparatus; the solutions are permanent; and the results are within 10 per cent of those obtained by much more elaborate methods.

CHAPTER XIII

Dietetic Treatment of Diabetes

If one surveys the history of the treatment of diabetes mellitus it becomes apparent that successful treatment, of certain patients at least, has been accomplished in seemingly diverse ways. It is now universally admitted that diet, and not drugs, is the mainstay of any successful treatment of this disease. At various times certain articles of food have been stated to have particularly beneficent properties in controlling the affection. These have had their vogue and have been followed by others for which in turn great things were claimed and denied. The points not generally recognized were—the total glucose content of these diets and the individual variations in the tolerance of different patients for these foodstuffs. Any foodstuff may be suitable for certain diabetics but this same substance may prove most harmful to others. For the less severe cases of diabetes mellitus dietetic control alone will effect a considerable improvement in their condition. For a certain proportion of cases no type of dietetic treatment is adequate in controlling the disease. For such patients "insulin" has been introduced into clinical use in conjunction with dietetic treatment. It may be said, however, that there is no case, whatever its severity may be, in which it will ever be advisable to use insulin without due attention to dietetic principles.

Diabetes is a disease in which the body is unable to efficiently metabolize carbohydrate. It has now been proven that this is due to insufficient insulin production by the pancreas. Insulin is apparently secreted into the blood stream by the Islands of Langerhans. A number of investigators, notably Opie, Allen and Conroy have called attention to the degenerative changes which occur in the islet tissue of the pancreas of severe diabetics. In partially depancreatized animals, Allen has demonstrated that functional and anatomical damage to the islet tissue results from overfeeding, thus indicating the necessity in treatment of keeping the work of the pancreas within the limits of its

capacity. The severity of diabetes is in direct relation to the patient's tolerance for "total glucose." This may be determined by placing the patient on a known diet and estimating the amount of glucose excreted in the urine. In calculating the total glucose content of the diet it must be remembered that it consists of 58 per cent of the protein and 10 per cent of the fat (the glycerine) as well as the preformed carbohydrate. When the diet is excessive, clinical cases of diabetes show evidence of damage to the pancreas in the reduced tolerance for total glucose which results. Rest to the pancreas must mean a reduction in the total glucose to be metabolized by the pancreas and the object of treatment should be to accomplish this result by suitable dietetic measures with or without the artificial administration of insulin.

Methods of treatment of diabetes having as a basic principle the reduction in the work required of the pancreas have been introduced by Allen and Joslin. Their methods of total dietary restriction and the use of fast days at intervals prolonged the lives of many severe diabetics, and the rest to the pancreas often resulted in an increased output of insulin, the internal secretion, and the greater tolerance for total glucose. This permitted of a more liberal diet being used. Though in certain cases of diabetes these methods have served admirably, it is unfortunately true that in other cases the necessary restriction in diet was so severe as to lead to marked undernutrition. Patients fed insufficiently are partly starved and the body protein and body fat are called upon to make up the minimal number of calories required to sustain life. The under-nourished, severe diabetic is quite unable to perform any useful work and is very subject to infections which may induce a further reduction in tolerance. In the most severe cases the "fasting" treatment actually defeats itself as the increased production of carbohydrate from body protein makes it impossible to get the patient aglycosuric. It would appear desirable to avoid these extreme degrees of undernourishment and to furnish the diabetic with a diet sufficient to satisfy his normal caloric requirements. It is apparent that in such a diet the carbohydrate and protein must remain low in amount since each of these require insulin for their combustion. It has been shown by Marsh, Newburgh and Holly that $\frac{2}{3}$ gram of protein per kilogram of body weight is sufficient to maintain nitrogenous

equilibrium provided the requirement for calories is otherwise met. The additional calories of the diet must be derived from fat but the complete combustion of this substance takes place only when sufficient carbohydrate is also being burned. When carbohydrate is markedly restricted from any cause, acetone bodies are produced from fat and in diabetics acidosis and coma may result. Woodyatt has suggested that 1.5 grams of fatty acid may be completely burned while 1 gram of glucose is undergoing combustion. Further work by Wilder and Shaffer appears to show that under certain conditions as much as 2 molecules may be burned with 1 molecule of glucose and no acetone bodies result. The relative efficiency of protein, carbohydrate and the glycerine of the fat in preventing acidosis has been well discussed by Shaffer. Plans for the dietetic treatment of diabetes based on the foregoing considerations have been suggested by Woodyatt and by Wilder.

Though in certain cases the ratio of fatty acid to total glucose may be markedly different, Woodyatt believes that in the long run a 1:1.5 gram ratio (1:1 molecular ratio) is the most satisfactory. Wilder has introduced a chart for calculating a diabetic diet on a basis of 1.7 molecules of fatty acid to 1 molecule of glucose in the food (ketogenic-antiketogenic ratio 1.7:1). Both these methods have a definite value in the treatment of diabetes mellitus. Some experience with the 1:1 molecular ratio made it apparent that too high carbohydrate tolerance was required to make it suitable for the majority of diabetics though most palatable diets might be constructed with it. The disadvantage of the Wilder ratio is that a large percentage of patients do not need it, that the ratio of carbohydrate to fat is very low, the choice of foodstuffs is thereby restricted and patients soon become tired of the monotonous diet. Of course some patients are encountered who will become aglycosuric only when on such a diet as Wilder's. But for the average patient a somewhat less drastic restriction is desirable. Only those who have seen it will appreciate the great difference a few grams of carbohydrate makes to these patients.

While recognizing the usefulness of varying the ratio of fat and total glucose in the diet in certain cases from any arbitrary standard, it seemed desirable to follow a method which would, to some extent,

avoid these difficulties. After trial, a molecular ratio of fatty acid to total glucose of 1.3:1 was adopted as being more generally suitable. The method to be described has been tried out during the past three years in the Toronto General Hospital. It has proved of particular service in connection with the insulin treatment of diabetes. It is now felt that such patients as are unable to remain aglycosuric and at normal blood sugar levels on this diet should be given insulin in suitable amount to accomplish this object.

The plan of procedure is to ascertain the normal basal caloric requirement for their age, height, weight and sex, and construct a diet with particular reference to the principles discussed above. The diet is calculated as follows:

1. The patient is weighed and his height measured.

2. From DuBois' Table (fig. 7) the surface area of the patient is obtained, and this when multiplied by the twenty-four hour basal requirement in calories for the patient's age and sex (fig. 7, Aub and DuBois) gives the normal basal caloric requirement for a patient at rest.

3. If the weight is obtained in pounds, inspection of table 6 gives the equivalent in kilograms directly, and this latter figure times $\frac{2}{3}$ gives the number of grams of protein required.

4. The basal caloric requirement (M) divided by 30, minus $\frac{1}{3}$ the protein in grams or, more simply, $C = \frac{M - 10P}{30}$ gives the number of grams of carbohydrate required.

5. Fat sufficient to make up the calories required is supplied by the formula, $F = \frac{M}{10} - \frac{P.}{2}$

Example: A diet is to be constructed for a man of 55 years, height 5 feet 7 inches, weight 132 pounds or 60 kgm.

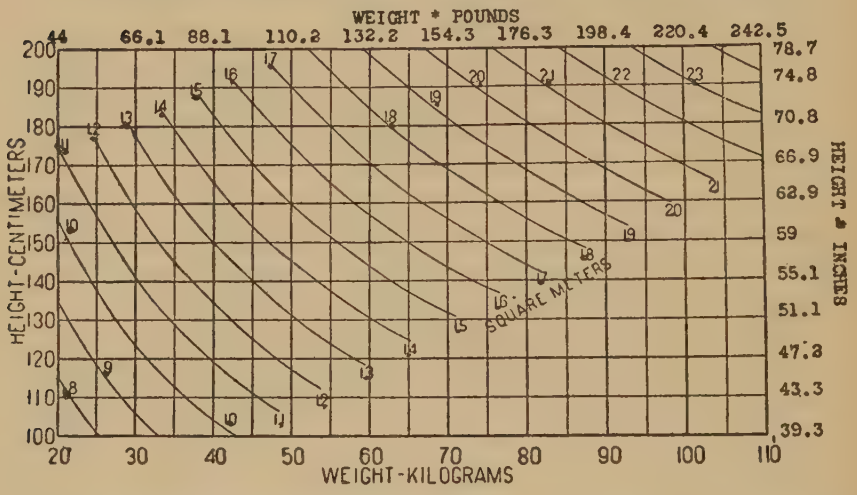
Inspection of table 6 shows a surface area of 1.7 sq. m. From table 7: $900 \times 1.7 = 1530$, the number of calories required per day (M).

The protein required $= 60 \times \frac{2}{3} = 40$ grams per day.

The carbohydrate, $C = \frac{1530 - 400}{30} = 37.6$ grams.

Fat $= \frac{1530}{10} - \frac{40}{2} = 133$ grams.

Surface Area Chart, Sq. M. (DuBois)



Caloric Requirement per square metre of body surface (Aub-Du Bois)

AGE	MALES		FEMALES	
Years	Cal. per Hour	Cal. per Day	Cal. per Hour	Cal. per Day
10-12	51.5	1236	50	1200
12-14	50	1200	46.5	1116
14-16	46	1104	43	1032
16-18	43	1032	40	960
18-20	41	984	38	912
20-30	39.5	948	37	888
30-40	39.5	948	36.5	876
40-50	38.5	924	36	864
50-60	37.5	900	35	840
60-70	36.5	876	34	816

Calculate requirement in children according to weight. Up to
10 kg. 55 cal. per kg.
10-15 " 50 " " "
15-20 " 50 " " "

Formulae for calculating food requirement in grams from Caloric Requirement (M) (W. R. Campbell)

P = 2/3 gm. per Kg. body weight.

$$C = \frac{M - 10P}{30}$$

$$F = \frac{M}{10} - \frac{P}{2}$$

Ex.: Male; age 55; Ht. 71 in. Wt. 154 lbs. S.A. 1.88 sq. m. 1.88 × 900 = 1692 cal. P=47, F=146, C = 40.6 gms.

FIG. 7. DATA FOR CALCULATING THE BASAL CALORIC REQUIREMENT AND THE PROTEIN, FAT AND CARBOHYDRATE OF A BASAL DIET

With the composition of the diet in terms of the weight in grams of protein, fat and carbohydrate required it is a comparatively easy matter to construct a suitable diet from food tables.[1] On such a diet, provided he is kept at rest, the patient, in the majority of cases, will become sugar free, though this is not usually accomplished as rapidly as in the starvation method. Acetonuria is also controlled but somewhat more slowly than by Allen's method. The advantage of the method consists in the increased comfort of the patient and the fact that, subsequent to getting the patient aglycosuric by the Allen method, a considerable period is required to determine the patient's tolerance. On this account the total period of treatment is actually shorter than the starvation method.

While the patient is in bed or confined to his room a diet equivalent to his normal basal requirement is sufficient. With greater activity a larger diet is required. Before any such increase is advised it is well to estimate the fasting blood sugar. Values of 0.13 per cent or over would seem to contraindicate such an increase, as patients with high blood sugar ultimately do badly. In most cases with a low blood sugar increase in the number of calories is the first object to be attained, and it is found that the addition of 5 grams of carbohydrates and 20 grams of fat, yielding 200 calories is a satisfactory method of increase as it provides a maximal number of calories without inducing ketosis. If this addition is well borne over a period of a week or more, a second and third increase in diet may be allowed, thus raising the food 600 calories above the basal requirement and restoring the patient to something like his old vigor. The ketogenic-antiketogenic ratio of these additions to the diet is 1.7:1, somewhat higher than the original ketogenic antiketogenic adopted for getting the patient sugar free but not higher than that based on Wilder's diet formula and quite safe so long as increases are small compared with the basal requirement.

Up to this time no additional protein has been used for three reasons:

[1] See page 194. Reference may also be made to Atwater and Bryant: Bull. 28, U.S. Dept. Agric., The Chemical Composition of American Food Materials; Joslin: The Treatment of Diabetes Mellitus; Locke: Food Values; Friedenwald and Ruhrah: Diet in Health and Disease, etc.

(1) it increases metabolism by its high specific dynamic action; (2) it is not as efficient an antiketogenic agent as carbohydrate; (3) the need for calories is greater. The diet at this point, though, is becoming somewhat top-heavy with fat and this means lack of variety in the menu. Variety can be provided by increasing the protein at this stage. It is thought that 8 grams of protein has about the same power to cause hyperglycemia as 5 grams of carbohydrate, and consequently this amount of protein plus 10 grams of fat is added to the diet. The ketogenic-antiketogenic ratio is 1.7:1, calories 122.

At this point a word of caution is worth while. The patient is now receiving 2252 calories, or 722 calories (40 to 50 per cent) above his basal requirement—sufficient for the performance of light work. It is the common experience that excessive work or excessive food intake ultimately results in reduction of the patient's tolerance for glucose and it is well to consider whether the increase in diet should not stop at this point. The activities of the patient do not require additional protein and it is believed that further increases in the diet should not be made unless the fasting blood sugar is normal. In such cases the diabetes will be comparatively mild and there is no reason to restrict the calories, protein, fat or carbohydrate to a greater extent than is necessary to maintain or attain normal body weight and maintain normal blood sugar levels.

The importance of maintaining low blood sugar levels in diabetes has never been overestimated and was never so clearly demonstrated as now. At the present time there is a tendency even under insulin treatment to neglect this important factor in the belief that increased insulin will take care of any further loss of tolerance which may develop. Nothing could be more fallacious. The greater the severity of the case, the nearer it approaches complete diabetes, the greater the difficulty of properly regulating the dosage of insulin and the time of its administration, the greater the number of hypoglycemic reactions encountered and the oftener the appearance of high blood sugar and glycosuria. In my experience and that of many others, it is unwise, considered from the standpoint of the ultimate result in treatment, to be satisfied with fasting blood sugar levels of more than 0.13 per cent.

Attention may be directed to the plan of increasing the diet slowly.

The period of relative rest to the pancreas has proved of value in promoting increase of tolerance for glucose in the sense referred to in the preceding pages (cf. page 122). Such a policy need not be followed in case the patient becomes promptly sugar free and other clinical evidence suggests that the tolerance for total glucose is much above the diet prescribed. Daily alterations of any considerable number of calories in the diet of a patient are unsound and in the long run waste time. The full effect of a given diet is usually not seen in less than three days even when blood sugar methods are employed and in perhaps 20 per cent of cases a week or more is required. To adequately treat and satisfactorily train the average diabetic patient in a week is in my opinion, impossible; to half-train him worse than useless. Nevertheless the experienced physician who carefully studies the individual patient may find opportunity for short cuts which accelerate the treatment. In such a case the general principles of treatment, ketogenic-antiketogenic ratio, etc., need not be rigidly applied but in doubtful cases adherence to the general plan of treatment is to be recommended as conducive to more rapid and more effective treatment. The patient who does not become sugar free on a diet equivalent to his basal caloric requirement requires insulin. It is improbable that he will ever be able to metabolize a working diet without insulin. The term of such a patient under immediate observation can be shortened by calculating a working diet and the dose of insulin required to metabolize it, placing him on it at once, and adjusting the insulin to produce a suitable blood sugar level. Any subsequent increases in tolerance will produce reactions, however, and the patient must be carefully trained to recognize and cure them himself.

It should not be forgotten that the most satisfactory results are to be obtained when the food taken is digested and absorbed. As pointed out by Woodyatt it is the metabolizing mixture of fats and glucose in the body tissues which determines the presence or absence of ketosis and this is borne out by clinical experience in the treatment of cases given improperly constructed diets in which marked disparity between the glucose and fatty acid obtained. With the damage to

the islet tissue of the pancreas there may be, and in severe cases often is, damage to the acinar tissue with deficiency of the external secretion of the pancreas, resulting in imperfect digestion of foodstuffs, and a totally different mixture being metabolized than is being fed. This possibility should not be lost sight of in the search for a cause of ketonuria in a case under treatment. In the more severe diabetics a morning ketonuria may be noted which disappears after 10 or eleven o'clock when the carbohydrate taken at breakfast is being metabolized. This ketonuria is never very serious but serves to remind us of the preferential utilization of carbohydrate over fat when both are available for energy production. It can sometimes be controlled by feeding a portion of the carbohydrate late in the evening. This procedure should be used with caution, however, since increase in the number of meals apparently increases the carbohydrate tolerance and one may be tempted to increase the patient's caloric intake in this way. Many devices such as, increased number of meals, small amounts of carbohydrate given an hour before the meals and active exercise after meals, have been employed to increase the carbohydrate tolerance. The improvement is more apparent than real, and is but temporary in nature. They cause a stimulation of the pancreas and more insulin is produced but the increased work injure the pancreas and ultimately lowers the tolerance of the patient for glucose.

When patients have passed through a period of undernutrition due to their disease or their previous treatment they very readily gain in weight when placed on a suitable diet. The diet here suggested is not actually the basal requirement of the patient but his calculated requirement under normal conditions. In reality severe diabetics, free from acidosis and on diets low in protein so that the specific dynamic action is low, have basal metabolic rates of 70 to 90 per cent of the normal; and this explains why patients placed upon such basal caloric diets actually gain in weight when they are relatively inactive. Within limits this increase in weight is desirable but it should not be forgotten that increased weight means increased caloric requirement and increased work for the pancreas. In the more severe cases it is felt that it is advisable to allow them to gain up to within 10 to 15 per cent of the average weight for their height and age. This is within the

normal variation and should provide a measure of protection against infection. The over-weight diabetic is advised to reduce in weight as his tolerance will improve by so doing. This may be done by keeping him on a basal maintenance diet and gradually increasing the work he is doing, or by supplying protein and carbohydrate as per formula and limiting the fat. If this is done care must be taken to avoid over-fatigue and should evidence of acidosis develop it should receive prompt attention.

Consideration must be given to the age of the patient in arriving at a suitable diet prescription for an individual, and other diseases must be considered in relation to their influence on the patient's condition. It is usually inadvisable to make radical changes in the diet of aged patients, especially if they are severe diabetics under their normal weight. The protein should not be too severely restricted in cases associated with myocardial incompensation. In these two groups of patients 20 grams more protein per day than usual is allowed. A third requirement for increased protein in the diet occurs in the child during the growth period. Here protein is required in larger amounts not only to replace more rapidly catabolizing tissue protein, but also to permit of growth of the child. If used for the latter purpose alone there seems no reason to believe that this protein *per se* increases the insulin requirement. Indirectly, however, by increasing the size of the child and providing a larger mass to be transported, kept warm, and supplied with nutriment, an increase in the internal secretion of the pancreas becomes necessary and due consideration should be given this factor in treating diabetic children. The quantity of protein allowed in our cases varies also somewhat with the age, from 1 to 2.5 grams per kilogram of body weight.

Instances of true chronic inflammatory renal disease associated with diabetics are, in the opinion of the writer, much less common than the literature would lead one to expect. The diagnosis has usually rested upon the presence of albumin, with raised blood-pressure, or cardiac enlargement; none of which are necessarily indicative of nephritis. When the latter is a real factor the limitations of his kidney function will have to be taken into account in treating the patient. The usual protein allowance ($\frac{2}{3}$ gram per kilogram) is advisable in those cases

showing a tendency to nitrogen retention. In other instances, where difficulty in excreting fluids and mineral salts are prominent factors, a limitation of the bulk of the food will be required. The more concentrated carbohydrate foods can be employed, thus limiting both salt and water intake. Infections in diabetic patients are always best treated on a diet liberal in protein, carbohydrate and calories, even if insulin should be required to keep blood sugar normal.

The diabetic diet should be made, as far as possible, from easily available, seasonable foods along the lines of a normal diet. It is much more satisfactory for the patient to obtain from among these natural foods at least the essentials of his diet than to be dependent entirely upon specially prepared diabetic foods. The latter are not only expensive but their obligatory use is an unnecessary and irksome social and business restriction which tends to make him dissatisfied with his treatment.

Consideration of a normal diet shows that it is commonly made up much as follows:

Breakfast

Fruit, e.g., grapefruit, oranges, etc.
Protein foods—eggs, bacon, fish
Cereal foods—porridge, bread
Fats—cream, butter
Non-nutrient substances—coffee, tea, etc.

Lunch

Soup
Protein food—meats, eggs, fish, etc.
Vegetables—potatoes, carrots, lettuce, beets, etc.
Fats—cream, butter, mayonnaise dressing
Desserts—custards, pies, fruit, fruit salad, etc.
Non-nutrients—tea, coffee, condiments

Dinner

Similar in composition to lunch

Monotony of diet furnishes one of the principal reasons why patients discontinue treatment. Yet it is astonishing to find how few altera-

tions in diet satisfy the normal healthy individual, a few changes sufficing to break the monotony. Diabetic patients should be specially trained and even urged to make for themselves the necessary changes in their diet. As certain foods are denied them the potentialities of change are indeed somewhat reduced but no diabetic with training and imagination need have exactly the same daily menu twice in ten years.

In the following tables (tables 6 and 7) are arranged a number of foods in common use with their approximate composition in protein, fat and carbohydrate, with weights and measures and other information useful to the diabetic. Table 6, which has been somewhat extended from a similar table by Joslin, classifies the vegetables and fruits according to their carbohydrate content. It will be noted that the 5 and 10 per cent vegetables are reckoned as containing 3 and 6 per cent of carbohydrate, whether raw or cooked. There is considerable variation in the actual carbohydrate content of these vegetables in different years and at different periods of growth and when grown on different land. Where, however, the diet includes several vegetables the average available carbohydrate content is sufficiently accurate. No attempt is made to calculate their actual protein content as it is comparatively small in amount and no accurate data exist. Attention may be specially directed to a list of non-nutrient substances including mushrooms, broths and mineral oil mayonnaise, which make most desirable additions to the diabetic dietary. Table 7 shows the protein, fat and carbohydrate content of various foods in a state ready to serve. Considerable variation in the protein and fat content of cooked meats may be expected, owing in part to their original composition, the size of the raw portion, and the method of cooking employed. Many of the values given have been derived from standard works on dietetics; others are from our own analyses. (See tables 6 and 7.)

Although the actual construction of a diet is time-consuming, and, at first, appears difficult, with a knowledge of the food value of the commoner foodstuffs and a little practice in arranging a diet the difficulty largely disappears. Worked out as suggested in the preceding pages, the basal dietetic prescription for a male patient fifty to sixty years of age, 5 feet 11 inches tall and weighing 154 pounds should contain 1692

TABLE 6

Approximate carbohydrate content of vegetables and fruits

5 PER CENT	10 PER CENT	15 PER CENT	20 PER CENT	NON-NUTRIENTS
Lettuce	Onions	*Green peas	Potatoes	Broths
Cucumbers	Squash	Artichokes	*Shell beans	Bouillon cubes
Spinach	Turnip	Parsnips	*Baked beans	Tea, coffee
Asparagus	Carrots	*Canned lima beans	*Green corn	Cracked cocoa
Rhubarb	Beets		*Boiled rice	Mushrooms
Endive	Kohlrabi		*Boiled macaroni	Salt, pepper
Marrow	Pumpkin			Sage, spices
Sorrel	*Canned green peas			Thrice boiled 5 per cent vegetables
Sauerkraut	Okra			Agar jelly
Beet greens	*Soy beans			Mineral oil mayonnaise
Dandelion				
Swiss chard				
Twice boiled carrots				
Twice boiled beets				
Twice boiled onions				
Twice boiled turnips				
Tomatoes	Lemons	Apples	Plums	
Brussels sprouts	Oranges	Pears	*Bananas	
Water cress	Cranberries	Apricots	Prunes	
Sea kale	Strawberries	Blueberries		
Cauliflower	Blackberries	Cherries		
Egg plant	Gooseberries	Currants		
Cabbage	Peaches	Raspberries		
Radishes	Quinces	Huckleberries		
Leeks	Pineapple			
String beans	Watermelon			
Broccoli	Muskmelon			
Macedoine	Twice boiled apples, dried prunes and peaches			
Celery				
Unsweetened pickled vegetables				
	Peaches canned in water			
Ripe olives (contain 20 per cent fat)				
Grapefruit				

Measures: 30 grams or cubic centimeters = 1 ounce. 1000 grams = 1 kgm. = 2.2 pounds. 1000 cc. = 1 liter. 1 calorie of heat raises the temperature of a liter of water 1° C. 1 gram protein or carbohydrate yields 4 calories. 1 gram fat yields 9 calories.

Reckon available carbohydrates in 5 per cent group as 3 per cent (3 grams of carbohydrates in 100 grams vegetables).

Carbohydrates in 10 per cent vegetables are reckoned as 6 grams per 100.

The percentage of carbohydrates in fruits is as indicated in the table.

Count clear soups and coffee substitutes as 1 gram carbohydrate per 100 cc.

* Denotes foods with considerable protein or fat. See table 7.

TABLE 7

Food values

Average amount per 100 grams unless otherwise stated

FOOD	PROTEIN	FAT	CARBO-HYDRATE
Bread, white Rolls	9		55
Shredded Wheat biscuit (1)	3		23
Cream of Wheat, dry	13		85
Oatmeal, dry Rolled Oats	16	7	67
Rice, dry	8		79
Rice, boiled	3		24
Macaroni, dry	13		75
Macaroni, boiled	3	1.5	16
Egg (1)	6	6	
Roast beet Pressed beef	23	28	
Boiled beef	25	23	
Steak, tenderloin	23	20	
Steak, round, lean	27	8	
Steak, sirloin	24	10	
Corned beef, canned	26	19	
Beef tongue, canned	20	23	
Veal, raw, leg, cutlet, loin	20	7	
Veal, roasted	28	1	
Mutton, roast	26	22	
Mutton, boiled, lean	31	5	
Mutton, chop, lean	22	5	
Lamb, roast leg	20	13	
Lamb, chop, broiled	22	30	
Pork, roast, lean	28	10	
Pork, chop, lean	26	6	
Pork, chop, fat	18	39	
Pork, steak	30	45	
Bacon, average raw	10	67	
Bacon, cooked, medium	15	40	
Ham, boiled, smoked	20	22	
Ham, fried	22	33	
Chicken, roast, young	25	5	
Chicken, broiler, raw	22	2	
Chicken, full grown	19	16	
Bass, raw	19	1	
Cod and haddock boiled	22		
Halibut, boiled	21	4	

TABLE 7—*Continued*

FOOD	PROTEIN	FAT	CARBO-HYDRATE
Salmon, boiled Salmon, canned	20	10	
Sardines, canned	23	20	
Trout, brook, boiled	21	2	
Trout, lake, raw	18	10	
Whitefish, raw	22	7	
Lobster, raw	16	1	
Oyster, solids	6	1	3
Shrimp, canned	25	1	
Milk, whole	3	4	5
Milk, skimmed	3		5
Cream, 16 per cent	2.7	16	3.8
Cream, 20 per cent	2.5	21	3.8
Cream, 24 per cent	2.2	24	3.8
Cream, 32 per cent	2	32	3.8
Cream, 40 per cent	1.8	40	3.8
Cheese, domestic	28	38	
Cheese, cottage	20		4
Butter Oleo		85	
Olive oil Salad oil Cooking fat		100	
Almonds, beechnuts	21	55	15
Brazil nuts	17	67	7
Peanuts	26	39	22
Peanut butter	29	46	17
Filberts, hickory nuts	15	66	13
Pecans	10	70	15
Walnuts	18	65	12
Dried peas, uncooked	25	1	57
Dried beans, uncooked	22	2	55
Dried soy beans	38	15	6
Green peas, cooked	5		15
Green corn, cooked	3	1	19
Banana (1)	1		20
Potato	2		18
Meat and vegetable stew	5	5	55

Values are for edible portion cooked or ready to serve, except as indicated.
For convenience, fractions of a gram are omitted.
Further tables of food values will be found on pages 194 to 203.

calories. Approximately this will be supplied by protein 47 grams, fat 146 grams, carbohydrate 41 grams; if the food is divided equally between the three meals, protein 16, fat 49, carbohydrate 13 + is the allowance per meal. To prevent ketosis during the early morning hours it is often useful to transfer a portion of the carbohydrate from breakfast to the evening meal. As the fats can be easily adjusted by varying the butter allowance, greater consideration is given to the carbohydrate, and next to the protein content of the foods. With the outline of a normal diet in mind, one proceeds to construct a diet for the patient in terms of the foodstuffs.

Breakfast. One hundred and fifty grams of grapefruit or 75 grams of orange or peaches contains 7.5 grams of carbohydrate. Two eggs will contain 12 grams of protein and 12 grams of fat in addition. Twenty grams of lightly cooked breakfast bacon will contain approximately 3 grams of protein and 8 grams of fat. The patient's diet now stands:

	AMOUNT	PROTEIN	FAT	CARBOHYDRATE
	grams			
Fruit, 5 per cent grapefruit or 10 per cent oranges	150			7.5
Eggs, 2 poached	75	12	12	
Bacon, cooked	20	3	8	
		15	20	7.5

Fifty cubic centimeters ($1\frac{2}{3}$ ounces) of 32 per cent cream (whipping cream) will supply 1 gram additional protein, 16 grams of fat and 1.9 grams of lactose, making the total of protein 16, fat 35, and carbohydrate 9.4 grams. The protein is suitable in amount; the fat can be balanced by adding butter (15 grams); and the carbohydrate is somewhat less than one-third the day's allowance. Tea, coffee, or cracked cocoa, bran cakes and, if necessary, agar jelly are added to provide extra bulk.

Lunch. Using the outline given for the noon meal, suitable quantities of the different foods are set down as for the breakfast. When

150 or more grams of fat are to be served it is useful to prescribe at least one cream soup, containing 30 to 60 cc. of cream and 50 grams 5 per cent vegetables, in the day. If cold meat is to be served the five per cent vegetables (150 to 300 grams) are served best as a salad with a mayonnaise dressing made with olive oil, or corn oil. In cases where constipation is a complication of the diabetes, liquid petroleum may be used in making the mayonnaise. For a cold lunch one may use a somewhat smaller portion of meat than when it is to be served hot, and the protein saved may be used in making a custard with eggs and milk or cream. Butter and cream together with non-nutrients may be added in suitable quantities.

Supper. In the evening meal hot meats and hot vegetables will usually be served. The general composition of the diet will be similar to the noon meal. A fruit salad may be used as a dessert or fresh sliced fruits or fruits canned in water may be served. To sweeten the fruit $\frac{1}{2}$ grain of saccharin is dissolved in 50 cc. of cream and the latter poured over the fruit after being whipped.

The following is the dietetic prescription completely worked out:

FOOD	AMOUNT	PROTEIN	FAT	CARBO-HYDRATES
		grams	*grams*	*grams*
Ration		47	146	41
Meal		16	49	13+

Breakfast

Grapefruit	150 grams			7.5
or orange	75 grams			
Eggs	2 grams	12	12	
Bacon, cooked	20 grams	3	8	
Cream, 32 per cent	50 cc.	1	16	1.9
Butter	15 grams		12.7	
Tea, coffee, bran cakes				
		16	48.7	9.7

Lunch

Soup { cream, 32 per cent	50 cc.	1	16	3.4
Soup { celery	50 grams			
Boiled ham	40 grams	8	8.8	
Salad (radish, lettuce, tomato, cucumber)	170 grams			5.1
Custard (recipe below)	1	4.5	5	4
Cream, 32 per cent	50 cc.	1	16	1.9
Butter	10 grams		8.5	
Tea or coffee, bran cakes, agar jelly, mineral oil mayonnaise				
		14.5	54.3	14.4

Dinner

Soup, clear	100 cc.			1
Roast beef	60 grams	13.8	16.8	
Vegetables, asparagus	100 grams			
Vegetables, marrow	100 grams			6
Fruit, 10 per cent	85 grams			8.5
Cream, 32 per cent	50 cc.	1	16	1.9
Butter	12 grams		10.2	
Tea or coffee, bran cakes, agar jelly				
		14.8	43.0	17.4
		45.3	146	41.2
Extra 10 grams cottage cheese with salad		2		0.4
Total		47.3	146	41.6

Pepper, salt and other condiments, q.s.: saccharin, maximum 3 grains per day.
Butter allowed, 37 grams.
Cream allowed, 200 cc.

In constructing the first draft of a menu it is unnecessary to use up all the protein, fat or carbohydrate assigned to any one meal, in that meal. Some slight latitude may be allowed if the whole day's ration approximates the correct total. Indeed it is often somewhat better to use slightly less than the prescribed amount of food, leaving a margin to be used as extras or garnishings to vary the diet. Vegetable salad tastes very different when enriched by the addition of a portion of lobster, a ball of cottage cheese, a sardine or a shrimp, or a small

slice of domestic cheese. Salted almonds or chopped nuts may be added to a fruit salad. The actual caloric value of these extras is almost inconsiderable, but they are of immense importance in increasing the palatability of the diet. In cases where the same foods occur in more than one meal (cream, butter, etc.) the weighing for the day is done before breakfast and suitable division of the food for the three meals can then be made.

The next problem arising will be the substitution of other articles of food for those occurring in the draft menu in order to avoid monotony of diet. The same quantity of any other 5 per cent vegetable (see table 6) may be substituted for those listed, or half as much 10 per cent vegetable may be substituted for the 5 per cent. Meats are substituted on the basis of their protein content, e.g., 60 grams roast beef containing 13.8 grams protein may be replaced by (1) 55 grams roast young chicken or (2) 51 grams lean roast pork, or (3) 51 grams roast veal, or (4) 69 grams of roast leg of lamb. In each case the fat content will vary somewhat from the value originally calculated (16.8 grams). The difference is adjusted by subtracting from the butter allowance or by adding sufficient butter (85 per cent fat) as necessary. Fourteen, 11.8, 16.3, and 7.8 grams respectively of additional fat are required in substituting the above meats for the roast beef on the menu.

In actual practice the available protein in a meal is compared with tables 8 to 10 which show the protein and fat content of different amounts of eggs, bacon, roast beef and ham. The weight of the portion with the most suitable protein value is set down in the original menu. The tables pages 186 to 194 then give the equivalent weight of other protein foods which may be substituted for it to give variety. Though the latter method is much simpler and quicker it is desirable that the patient understand the longer method as well. Table 22 shows a list of desserts which may be substituted for a diabetic custard (recipe, p. 174).

Where a food containing protein and fat and carbohydrate is to be used as an alteration in diet substitute it for a carbohydrate-containing food adjusting the protein and fat content of the diet by increasing or decreasing the meat and butter as necessary. Simple variations in a

diabetic diet are learned without difficulty by making and writing down one variation per day. During the growing season care should be taken to use freely of the more perishable foods, leaving those which are easily preserved for winter consumption.

A basal maintenance diet only provides the energy required by the patient at rest. Additional food will be required if the patient is to return to his work. The increase in food intake is best made gradually, and the effect on glycosuria and the blood sugar observed. Five grams of carbohydrate and 20 grams of fat is a suitable quantity in many cases. One hundred grams 5 per cent vegetables, 50 cc. 32 per cent cream, and 5 grams of butter may be used. The gram of protein in the cream may be allowed for by cutting out the 10 grams of cottage cheese. With slow successive increases, with or without insulin, the character of the diet is gradually altered, new foods becoming available with the rising carbohydrate allowance. If, for instance, the above basal diet is to be raised to protein 47 fat 186, carbohydrate 51, a 15 gram portion of oatmeal (weighed dry) may be introduced. This will contain protein 2.4, fat 1, carbohydrate 10 grams. Decrease the grapefruit allowed to 100 grams. Discontinue the cottage cheese and add 75 cc. 32 per cent cream which equals protein 1.5, fat 24, carbohydrate 2.9. Decrease the roast beef to 50 grams to balance the protein and add 22 grams of butter to balance the fat. Another method of altering the original menu would be to discontinue the grapefruit and the cottage cheese and add to the breakfast 15 grams oatmeal (weighed dry) and 125 grams 5 per cent vegetable, e.g., fried vegetable marrow or tomatoes, and increase the daily allowance of cream by 100 cc. and of butter by 10 grams. Increase in the protein allowed is not necessary for the performance of work. When one constituent of the diet is noticeably small relatively to the other, however, there is a certain difficulty in balancing the diet. For this reason, when the caloric increase is approximating the requirement for work it is desirable to increase the protein of the diet. This is most simply done by increasing the amount of meat allowed during the day and rebalancing the fat by adding or subtracting from the butter allowance. More elaborate made dishes may be introduced into the diet when the patient has shown himself capable of calculating the simpler diets.

As, in the diabetic dietary, many of our cheaper staple foods are prohibited or, at least, greatly restricted, the patient's food becomes more costly than the diet of the average normal person. In some instances, it will be necessary to consider the expense in constructing his diet. The diabetic who regains his earning power, should be advised to spend liberally for his own food and thus avoid the monotony of diet and dissatisfaction attendant upon the use of the cheapest available foods. Intelligent marketing will help to solve the problem, but in case the poorer qualities of food are inevitable, much may be done by suitable culinary methods to make them palatable. Skilful alternation of the foods, the employment of different methods of cooking, roasting, pot roasting, baking, frying, broiling, steaming, the use of seasoning agents, etc., may be invoked to improve the flavor of the cheaper foods. Lack of knowledge, time and care in the preparation of the food rather than its quality is the essential cause of dissatisfaction with most meals.

Insufficient attention has been paid to the value of non-nutrient substances in the diabetic dietary. In reality one depends upon these substances to a considerable extent for flavoring the food and tempting appetite. In many undernourished cases of diabetes the bulk of these substances gives a comforting sense of fullness after meals, which definitely contributes to the feeling of well-being of the patient. In addition, however, the severe diabetic showing glycosuria tends to become dehydrated and thereby suffers from marked constipation. The unabsorbable residues of these non-nutrient foods tends to relieve this condition. When the diet has been increased to a sufficient amount the bulk may be decreased with advantage.

The introduction of insulin permits the severe diabetic to make use of a more satisfactory diet than formerly. While it does not confer a power of unrestricted choice on the patient it is now perhaps unwise to feed him less than 50 grams of carbohydrate per day over long periods of time. On such a diet oatmeal may be used. Ten grams of carbohydrate are contained in a small portion (15 grams dry weight) and this forms a satisfying addition to the menu. If desired, some washed bran may be added during the cooking to increase the bulk. The amount of bread allowable to severe diabetics is only an aggrava-

tion. I would agree with Joslin that the severe diabetic should forget the taste of bread. The non-nutrient bran cake (see recipes) is very palatable and furnishes a vehicle for the butter allowed. If consumed in excessively large amounts, however, it leads to discomfort from intestinal fermentation. Provided the expense is not a barrier, "Cellu" flour or "Nutrivoid" flour may be mixed with the washed bran. In less severe cases (carbohydrate tolerance of 70 grams or more) small amounts of bread may be allowed with advantage if the patient be carefully supervised. White bread is preferable to brown bread since cane sugar and molasses are often used in the latter. Several preparations made from soy bean or casein are on the market. These make rather palatable bread substitutes but have the disadvantage of very high protein content. Most patients abandon them for an equivalent amount of meat. Gluten flour has a limited value in the milder cases of diabetes. Its protein content is rather high and the carbohydrate content very uncertain. If used, the flour may be mixed with washed bran and made into muffins which are fairly palatable.

In most cases it will be found advisable to institute treatment in a hospital rather than under home conditions. Much more dependence can be placed on the results obtained when the food is weighed, cooked and served by experienced assistants and the patient receives a practical demonstration in methods which are invaluable to him. As the diet is increased he should be encouraged to take more exercise and when he demonstrates that he remains at a normal blood sugar level on a maintenance diet he may be treated as an ambulant case. A diabetic patient should be taught at least the essential facts about his disease: how to construct his own menus, how to prepare the less familiar foods, how to test the urine for sugar and diacetic acid, and how to weigh his food. Several suitable scales can now be procured with which the weighing of the food can be done with a minimum of trouble. The advantages gained are not alone the exactitude in the patient's intake of food; the mental discipline and training increases the patient's morale. He early observes the effect of relaxing his vigilance and learns to obey the restrictions necessary for the treatment of his condition. The treatment of severe diabetics without weighed diets is disastrous. A relatively short experience will con-

vince any competent observer of this fact. Mild cases may, it is true, be able to remain sugar free on a qualitatively restricted or even a

TABLE 8

Protein and fat content and caloric value of eggs and lightly cooked bacon

	PROTEIN	FAT	CALORIES IN PORTION
	grams	*grams*	
1 egg	6	6	78
1 egg and bacon, 15 grams	8.2	12	141
1 egg and bacon, 20 grams	9	14	162
1 egg and bacon, 25 grams	9.7	16	183
1 egg and bacon, 30 grams	10.5	18	204
2 eggs	12	12	156
2 eggs and bacon, 15 grams	14.2	18	219
2 eggs and bacon, 20 grams	15	20	240
2 eggs and bacon, 25 grams	15.7	22	261
2 eggs and bacon, 30 grams	16.5	24	282

TABLE 9

Protein and fat content and caloric value of different weights of cooked roast beef

WEIGHT	PROTEIN	FAT	CALORIES
grams	*grams*	*grams*	
30	6.9	8.4	103.2
35	8	9.8	120.2
40	9.2	11.2	137.6
45	10.3	12.6	154.6
50	11.5	14	172
55	12.6	15.4	189
60	13.8	16.8	206.4
65	14.9	18.2	223.4
70	16	19.6	240.4
75	17.2	21	257.8
80	18.4	22.4	275.2
85	19.5	23.8	292.2
90	20.7	25.1	308.7
95	21.8	26.6	326.6
100	23	28	344

guessed diet, but in such cases there is a great tendency to exceed the limitations and to neglect urinary examination, etc. Unless kept under careful observation a patient may persuade himself that

he is cured and relax all restrictions. The loosely treated diabetic is a menace not only to himself but to other diabetics with whom he comes in contact.

The construction of diets may be summarized as follows:

1. Obtain the diet prescription suitable for the patient by determining the caloric requirement from the chart (page 126). From the formulae determine the amounts of protein, fat and carbohydrate required.

TABLE 10

Protein and fat content and caloric value of different weights of boiled ham

WEIGHT	PROTEIN	FAT	CALORIES IN PORTION
grams	*grams*	*grams*	
30	6	6.6	84
35	7	7.7	97
40	8	8.8	111
45	9	10	126
50	10	11	139
55	11	12.1	153
60	12	13.2	167
65	13	14.3	181
70	14	15.4	195
75	15	16.5	209
80	16	17.6	222
85	17	18.7	236
90	18	19.8	250
95	19	21	265
100	20	22	278

2. Divide the diet allowance into three meals.

3. Model the menu along the lines of a normal diet, giving first attention to the carbohydrate portion and then to the protein.

4. Having found the protein available for the meal, set down eggs and bacon for breakfast, roast beef for lunch and ham for dinner in amounts having a suitable protein content. See tables 8 to 10. Tables 11 to 23 will then give a list of substitutes for these.

5. Balance the fat column by adding butter or oil.

6. Add suitable non-nutrient substances.

CHAPTER XIV

Insulin Treatment of Diabetes

With insulin the principles guiding treatment of diabetes remain the same save that they may now be carried out more effectively in the more severe and even in the most severe cases than was previously possible. The aim in treatment of the diabetic should be the restoration of the ability to work, at the same time safeguarding the damaged pancreas by maintaining the patient's blood sugar at normal levels. The majority of patients may be made aglycosuric by undernutrition, low protein diets, high fat diets, exercise, or even by less drastic measures, but these partial successes are insufficient. In addition, these patients may be restored to more normal life by more suitable dietetic measures, or if these prove insufficient, by the administration of suitable quantities of insulin. It is generally agreed that insulin should not be employed unnecessarily because of the risk of hypoglycemia, the inconvenience and discomfort of the daily injections, the greater strictness required in balancing the diet with the insulin administered and the expense of the treatment. It is far better, however, that the patient who needs it should use insulin so that he may work, to purchase more insulin, with the better food, greater variety of food, greater strength, greater freedom from infections, and greater happiness that goes with it than merely remain alive, a dismal burden to himself and his friends. Insulin has its dangers; it also has many advantages. In most cases by careful investigation and careful treatments its use may be avoided but the same kind of investigation of the diabetic patient furnishes a sound basis for treatment with insulin when that appears desirable. The careful history and examination, treatment and care of associated conditions, training in hygienic measures, dietetics, uranalysis and investigation of his tolerance for food are necessarily associated with any sound treatment with insulin. Various methods have been brought forward by different authors and

doubtless there will be considerable difference of opinion with regard to the diet and the use of insulin until much more information on these subjects has been acquired. Based on the plan outlined for dietetic treatment in the preceding chapter the indications for the treatment of diabetes mellitus with insulin and diet become clear cut and simple. The treatment of acidosis and infections has been discussed elsewhere

When a patient is able to consume a diet containing a considerable amount of protein and carbohydrate without raising his blood sugar level or causing glycosuria there seems no reason for unduly restricting him, though he should be instructed in the elementary facts concerning the disease, dietetics, etc. The more severe the case the more necessary it becomes to restrict protein and carbohydrate and to depend in greater measure on fat as source of energy. It is in these cases that a knowledge of safe, and at the same time palatable ratios of fat to the total glucose of the diet becomes of importance. When a patient placed on such a diet as outlined in Chapter XIII fails, after several days' trial, to become sugar free he needs insulin both for metabolizing that diet and any further increases he may need for working purposes. Should he become promptly sugar free he will in all probability not need insulin. If he becomes sugar free only after several days of dietetic treatment he may require insulin to metabolize a working diet. Certain of these cases, however, acquire a somewhat greater tolerance after a further period of dietetic treatment and may escape use of insulin after a more or less prolonged dietetic treatment. Most of such cases show morning fasting blood sugars in the normal band (0.08 to 0.12 per cent), and if slight glycosuria occurs it is a postprandial symptom. Such patients are often excessively sensitive to the sugars, and substitution of five per cent vegetables for the fruits or high percentage vegetables in the diet may be sufficient to cause cessation of the glycosuria. Patients who slowly become aglycosuric on their basal caloric requirement, but have fasting blood sugars of 0.15 per cent or even 0.14 per cent, will require insulin to metabolize sufficient additional food to do work and to reduce their blood sugar to normal. Those patients who become sugar free but show persistent glycosuria on increase in the diet should be given insulin sufficient to raise the diet to the working level.

It has been recommended by several investigators that insulin should be given in gradually increasing doses from the beginning of treatment. This method converts a large number of patients who can do without insulin into insulin cases, as the pancreas apparently ceases to produce as much insulin for a time. The patient however is often the victim of a very severe reaction at a later period. Other authors favor testing the patient on a diet, and if he fails to become aglycosuric they advise insulin in slowly increasing doses until the patient's urine becomes sugar free. If carried out sufficiently slowly the method is fairly satisfactory. Daily increases in insulin dosage, however, are not satisfactory, as patients do not respond so rapidly to diet alterations, pancreatic rest, or the effects of a given dose of insulin. Changes should not be made more often than twice weekly, and such treatment becomes very prolonged. We prefer to test out the patient's tolerance to a basal diet and determine the necessity for insulin in that individual, and then, if insulin is necessary, to render the patient aglycosuric immediately by a suitable dose of insulin. The dose of insulin required to make a patient aglycosuric will naturally vary with the tolerance of the individual for the diet. The amount of sugar excreted falls to a fairly constant amount and from the average quantity of glucose excreted per twenty-four hours is determined the desugarizing dose of insulin. $\frac{\text{Grams glucose excreted}}{1.5}$ = units of insulin required per day. (See page 81.) The insulin is usually administered in two doses in the half hour preceding breakfast and the evening meal, since it then relieves the work of the pancreas at the period of greatest overload, the period of absorption of carbohydrate. The less severe cases will become promptly sugar free on such a dose. The more severe and especially the aged arteriosclerotics may respond more slowly, and in a few cases the dose will have to be increased. In most cases the amount of insulin given will be too large for continued treatment, and it must then be reduced. $\frac{\text{Grams glucose excreted}}{2}$ gives a more suitable dose for prolonged treatment. As the patient will require a larger amount of food if he returns to work it is perhaps unnecessary to reduce the insulin dose, but instead the diet is increased a suitable amount to

cover the excess insulin. An increase in diet of 5 grams of carbohydrate and 20 grams of fat is equivalent to about 4 units of insulin. Patients who become sugar free on the original dose of insulin, but maintain high fasting blood sugars are more severe than the average, and their diet should not be increased without a corresponding increase in insulin. Indeed, the amount of insulin for an increase in diet may be calculated (see page 81), and the two processes may be carried out together. Further increases in diet may be made, increasing the insulin simultaneously or not according as the patient gives evidence of requiring more insulin, or shows an increase in tolerance for glucose by increases or decreases in the height of the fasting blood sugar level.

Since the object of treatment is to raise the diet to a working level, it might be conducive to more rapid treatment if the total working maintenance diet were given immediately after the patient becomes sugar free, and the insulin required to metabolize it calculated and administered. When an aged patient or a patient with long standing well-treated diabetes requires insulin to metabolize his food, it is rather unlikely that he will show any increase in tolerance, though exceptions are not wholly lacking to this rule. Danger from hypoglycemia due to spontaneous increase in tolerance in such cases is practically negligible. On the other hand they usually require somewhat more insulin to bring their blood sugar to normal on the new diet than the average patient. In cases selected judiciously a considerable saving of time is effected by adopting this method. In less severe cases in young adults, diabetes of short duration, or those overweight diabetics who need insulin, the adjustment is likely to be less satisfactory and much time may be wasted readjusting the insulin dose because of changes in tolerance. Such a patient as develops a late improvement in tolerance may have a severe reaction after he has been discharged from immediate observation. On the whole, because of numerous failures to adjust the insulin with such a large amount of additional food at one time, one prefers to adopt the somewhat slower step-like increase in diet suggested in the preceding chapter, with increases in the insulin dosage if indicated.

Patients who become sugar free on a basal diet but show persistent hyperglycemia while fasting will in all probability develop glycosuria

if allowed a maintenance diet. Sufficient insulin to lower their blood sugar (2 units for each 0.01 per cent in excess of normal) and sufficient insulin to metabolize the dietary increases should be given. Many of these patients will subsequently require less insulin and mild symptoms of hypoglycemia should be carefully watched for in order to avoid the more severe reactions.

Before discharging any insulin patient from immediate observation the blood sugar should, if possible, be stabilized at the normal level. In most cases this will have been done during the treatment, but if not properly adjusted when the working diet has been reached the dose of insulin should be raised or lowered to bring the fasting blood sugar within the normal band (0.08 to 0.12 per cent). For most cases this is easily done but particularly among the aged arteriosclerotic diabetics there are found some patients whose threshold of excretion for glucose is high. These patients tend to have an hyperglycemia which is very resistant even to large doses of insulin. It is possible that such cases require a somewhat higher blood sugar level than the normals. If treatment with high insulin dosage is continued these patients may sometimes suffer from severe unexpected hypoglycemia and it is perhaps unwise to attempt too much in such cases. We have noted that if given insulin in slight excess of the amount required to maintain the fasting blood sugar at its stable level the level slowly falls in many cases.

In patients requiring insulin the best prospect of recovery of tolerance is found among those who are given sufficient insulin to keep the blood sugar normal and who are not given an excessive number of calories. While the mild diabetics may often be able to tolerate considerable quantities of carbohydrate and a high calorie diet when their blood sugar is normal, the amount of carbohydrate and calories tolerated decreases with the severity of the disease. Few, if any, insulin diabetics should receive more than 2500 calories per day. This, of course, puts a limit on the amount of work such a patient can do, and in some cases necessitates a change of work to the lighter forms of occupation. Patients in the more sedentary occupations or professions may be adequately nourished and carry on their work as usual, but the carpenter should attempt only inside finishing, stair building,

etc., or become a cabinet maker, and so on. The blacksmith will obviously not receive sufficient calories for his work; the farmer must supervise his farm or adopt dairying, fruit growing, or poultry raising, etc. The casual laborer is the most difficult economic problem. A certain proportion of them may become motormen, waiters, footmen, janitors, chauffeurs and handy men, but in a considerable number of cases we have to appeal to the social service agencies to procure for them posts as elevator men, watchmen, store keepers, and so on. As women naturally adopt the lighter type of occupations we have encountered few who could not return to their former work, though it is questionable whether they should accept such nerve racking posts as, for instance, that of a telephone operator or positions of great worry or responsibility. Domestic service seems a satisfactory occupation but charing by the day or work as a laundress is rather too severe labor for severe diabetics requiring insulin treatment.

In preceding chapters the method of administration of insulin and the dangers of insulin have been discussed. In addition to the other information which the patient treated by dietetic measures must assimilate and understand before he can graduate as a trained diabetic, the insulin treated diabetic must be thoroughly impressed with the possible danger of insulin, hypoglycemia, its causes, symptoms, prevention and cure. He must also be trained in the measurement and administration of his own insulin, the sterilization and care of the needles and syringes, etc., before he is a safe person to entrust with his own life. He should further be impressed with the danger of discontinuing insulin when not under supervision. While we object to the unnecessary use of insulin and believe that, as a general rule, few patients for whom insulin is advised should ever discontinue its use there are occasions such as pre-operative preparation, infections, etc., where its temporary use or temporary increase in dosage is advisable. Reversion to the previous condition should always be carried out under supervision of the physician. A gradual diminution of the dose may be made without danger if regular daily tests for sugar and diacetic acid are being performed. If high calorie diets have been used and particularly if the amount of fat in the diet has been large, reduction of diet should accompany the diminishing insulin dosage. Should a

patient accidentally run short of insulin he should communicate with his physician and every effort should be made to provide it as soon as possible. In the meantime the patient should immediately go to bed, take liberal amounts of fluid (water, tea, coffee, broth) and reduce all the constituents of the diet by one-third, or if considerable quantities of fat are being used the latter may be even more drastically restricted. Resumption of the usual diet may be made when a new lot of insulin has been procured. The discontinuance of insulin with retention of the high calorie diet has been promptly followed by acidosis and coma in a considerable number of cases reported in the literature.

Many patients and, unfortunately, some physicians appear to beleive that temporary courses of insulin and strict dietetic measures will atone for carbohydrate "sprees" and general neglect of treatment but this is not the fact. It has been so clearly shown that even temporary carbohydrate excess has a temporary and too often permanent effect on the patient's tolerance that it is, in my opinion, unjustifiable to perform a blood sugar tolerance test on a known diabetic. In true diabetes mellitus carbohydrate excess, if prolonged, inevitably spells loss of tolerance both for carbohydrate and calories and further damage to the insulin producing function of the pancreas. A delicately balanced mechanism for supplying the adequate amount of insulin required from minute to minute cannot be exactly replaced by the subcutaneous injection of insulin solutions, once, twice, or thrice a day though the larger the number of injections, if suitable quantities are used, the more perfect the imitation of the normal process becomes. Were it possible to produce a very slowly absorbable insulin complex it would still fall short of the normal process in point of adaptation to the quantity required at different periods of the day, or to metabolize carbohydrate eaten between meals or at unusual times. Fortunately few patients have entirely lost the power to manufacture some insulin and this allows of a slight degree of latitude in the treatment of a patient. Insulin solutions may be injected to cover the "peak load" allowing the patient to devote his own insulin to that portion of the day which is not adequately supplied with the artificial product. As the insulin production falls even the ability to maintain normal blood sugar levels apart from the absorption period for food becomes di-

minished and artificial insulin must be supplied for this purpose as well. This cannot be adequately carried out even in conjunction with the strictest dietetic treatment and the patient finally may reach the stage where hypoglycemia from large insulin dosage alternates with hyperglycemia and glycosuria, a most difficult as well as most dangerous type of diabetes to treat. Insulin must always play a subordinate rôle to dietetic treatment in diabetes. Frank recognition of it as a therapeutic crutch and not a cure for diabetes in no way detracts from its very great value in the treatment of the disease, its preëminent value in diabetes complicated by acidosis and infections or its importance in the investigation of the problems of intermediary metabolism.

CHAPTER XV

General Effects of Insulin

The physician has numerous criteria by which to judge the progress made in the treatment of the diabetic. Though it is desirable, in most instances, to teach patients as much as possible about their disease the patient himself is prone to judge his progress by his subjective sensations and the general condition of his body. With dietetic treatment in the less severe cases marked improvement was possible and some improvement nearly always occurred. With insulin the more severe diabetic whom previously we considered ourselves fortunate to be able to keep alive, has attained to a state of general health approaching the normal (68, 69). With increasing strength the patient not only loses the sense of weakness and continuous state of fatigue but muscle activity becomes a joy to him. Dryness and harshness of the skin and hair disappear. Skin infections clear. Allen (75) seems of the opinion that infections are more frequent in patients under insulin treatment than on under-nutrition diets. This may have been true in hospital practice if care was not taken to isolate diabetics from other persons having infections. It is most certainly not so in our experience in the home, nor in hospital practice provided the same care is exercised to prevent hyperglycemia as was the case when dietetic treatment alone was available.

The insatiable hunger of the emaciated, under-nourished, diabetic disappears with the improved state of nutrition, and is replaced by a healthy appetite for regular meals. We have found that the menstrual function has returned in several instances; so also, occasionally has sexual desire. Eyesight usually improves in those cases with lesser degrees of local damage. The restoration of physical vigor is such that most patients are able to return to work. Most interesting is the change in the mental state of the patient. From depression, melancholia, inability to think, and often black despair, patients

recover to an astounding degree their mental alertness, cheerfulness and interest in their surroundings. Irritability and insomnia disappear.

Previous to the use of insulin the carbohydrate tolerance of a patient was known to improve under suitable treatment. This was not at all dependent upon a mysterious beneficent influence of under-nutrition but upon adequate attention to the principle of rest to the damaged and overworked pancreas. It probably was true that in some patients with a low tolerance the pancreatic function was rested by under-nutrition and that their tolerance improved thereby. It cannot be too emphatically stated, however, that all grossly under-nourished patients did not derive this benefit and, consequently, were worse off than before the treatment was undertaken. On the other hand many patients, adequately nourished and in whom the blood sugar was carefully maintained around normal values, exhibited as marked increases in tolerance or endogenous insulin production as starved patients. Other cases, whether under-nourished or not, have developed a fixity of tolerance which is unaffected by treatment. The difference probably lies in the degrees of damage existing in the pancreas. In some cases the degenerative process may have reached a stage where healing takes place only by loss of functional tissue and in others partial restoration of damaged cells may have occurred.

Insulin provides for some patients an opportunity for resting the pancreatic function, which was impossible by other methods of treatment, and as a result increases in tolerance are not uncommonly observed. As the majority of the Toronto cases have been selected from the class of patients with long continued, severe diabetes it is natural that we have not seen so great a return of tolerance as other investigators. The proportion of patients with uncomplicated diabetes who find it possible to discontinue insulin after a time is comparatively small, but many show an increase in tolerance which though small is yet sufficient to render it possible to supply a working diet with the same dose of insulin as was previously necessary when only a basal maintenance diet could be given. In some cases the insulin dosage may even be reduced. It seems possible that this so-called recovery of tolerance which usually occurs in the first months after

treatment with insulin should be regarded rather as release of a latent tolerance submerged by previous overwork of the pancreas.

The question of an actual regeneration of islet tissue must be very cautiously approached. It can be settled only by time and it seems unfair to arouse hopes that are not justified by experience. In some of the mild cases and particularly in the young this is a possibility. It may be pointed out that children, who have not attained adult body weight, present the additional possibility that, under careful treatment and rest of the pancreas with insulin, a normal growth of the pancreas with increase in age may occur and thereby a greater tolerance for carbohydrate may be acquired. Close observation of some cases is being made to determine these points and the work of Drs. Boyd and Robinson showing actual new islet tissue growing in a child's pancreas is most encouraging. Whether we are preventing diabetes in cases of acute pancreatitis with glycosuria and acidosis by administering insulin and reducing the diet it is impossible to state with any certainty. Some of the cases, before the days of insulin, recovered on a reduced diet, while others became true diabetics. An interesting and unexpected development in four cases of pancreatitis with glucosuria was the marked reduction of pain after the administration of insulin. Further observations are necessary.

BODY WEIGHT

Increase in the body weight of diabetics to any desired level can now be induced under insulin treatment. It should be pointed out, however, that in this case as in so many others, insulin merely makes possible for the severe case of diabetes a condition which is possible under suitable dietetic regimens in the patient afflicted with the milder forms of the disease. To many the evidence of the scales may seem a guarantee of progress but this is only true if one realizes the source of the weight change in the particular patient. We may dismiss at once the question of restoring to the obese diabetic the few pounds he has lost since there can be no question that overweight is not a favorable condition. The obese diabetic needs a fat reduction cure even more than the corpulent, middle-aged candidate for diabetes. In the former case the damage has been done but this is usually moder-

ate in degree as far as tolerance for carbohydrate is concerned. Reduction in weight increases the effective mass of active pancreatic islets relative to the size of the individual and thereby relatively increases the tolerance of the patient. The man of forty-five, 5 feet 10 inches tall, who is 40 kgm. over-weight requires, merely to live, 350 calories more than if he were of normal weight. In addition, of course, he must expend energy to carry the superfluous fat. Reduction in weight in such cases should not, of course, involve loss in muscle mass or muscular efficiency.

Probably the most spectacular increases in weight, following insulin, occur in patients suffering from marked emaciation, acidosis and dehydration. In these cases it is easy to see that the increase in weight cannot be due to deposition of protein since insufficient of this food principle is ingested. Since the deposition of fat in the body is accomplished in almost an anhydrous manner, only 10 per cent of its weight of water being required in the process, the weight increase cannot be due to fat which is also insufficient in amount. The deposition of carbohydrate in the body is accompanied by three times as much water. The limited possibilities of glycogen storage, however, make it unlikely that much more than a kilogram increase in weight can be expected from this source. An approximate balancing of the total fluid intake and output gives the clue, namely: that the weight increase is largely due to water retention. The type of diet served the diabetic is rich in mineral salts and these assist in maintaining a normal osmotic pressure in the tissues and the diabetic quickly attains a plump appearance, while the tissue turgor is distinctly increased. As Allen and Joslin have remarked, this affects particularly the face of the patient, but the whole body is involved to a greater or less extent. If sodium bicarbonate is also used this tendency may become very pronounced. The amount of weight increase in emaciated patients due to stored fluid without edema may be quite astonishing. Twelve pounds is not an uncommon amount for such a diabetic to store, but the adult in good nutrition will probably store less fluid. Even here the weight increase attainable without edema may be considerable. In experiments on water drinking the writer found six pounds increase in weight after the diuresis, due to drinking ten litres of water, had

ceased. This increase in weight persisted for several weeks without evidence of edema or change from the original values in either hemoglobin, red-cell count or blood pressure.

In some cases where the fluid intake of emaciated patients was not sufficiently controlled edema developed. In ambulant patients this has been most striking and is due to change in position of the excess body fluid rather than in excess intake of fluid immediately before. In twelve hours a patient may lose the plump facies and become pinched, drawn and emaciated while examination reveals marked edema of the ankles and legs. The reverse change occurs in dehydration. This change in the condition of the tissues is not wholly due to a true loss of body fluid but may occur fairly rapidly when no urine is being secreted, and in spite of moderate fluid intake.

True increases in body tissue are acquired comparatively slowly. Emaciated patients fed with fat in excess of their needs may indeed store it but it is questionable whether increase in weight due to an inactive substance like fat is desirable beyond a certain point. An increase in total muscle mass or other tissue containing protein serves a useful purpose. The supply of essential body fluid to replace that lost is also desirable but it is important to realize that fat and excess fluids merely contribute a cosmetic effect and require energy to keep them warm as well as to move them about. The patient whose body weight is between normal and 15 per cent below normal is the most satisfactory risk.

In treating the obese diabetic it is our policy to induce a fall in weight provided myocardial disease is not a complication. The diet prescription is calculated as previously described from the basal caloric requirement and 10 to 15 grams of carbohydrate are added in order to prevent ketosis. The protein is usually two-thirds of a gram per kilogram body weight, though sometimes the ideal weight for the individuals' height and sex is taken. Much reduction in protein appears to make the patient feel weak. The fat content of the diet is decreased by 25, 50 or even 66 per cent and exercise is encouraged so as to increase the caloric deficiency. Bulk is supplied to the diet by using 5 per cent or thrice boiled 5 per cent vegetables. Many patients lose considerable weight rapidly on such a régime, principally due to loss of water. The

later rate of weight loss is decidedly slower and it is, as a rule, inadvisable to have a diabetic patient lose weight rapidly on account of the feeling of weakness developing from loss of muscular strength. Bodily massage, particularly abdominal massage (with the patient as the operator), appears to be of some value in mobilizing fat from the connective tissue stores.

The undernourished diabetic patient, on the other hand, should not be encouraged to gain weight rapidly even though he may do so fairly safely by eating large quantities of fat. These patients suffer from lack of strength. An adequate number of calories for existence plus moderate activity, care that the blood sugar level is kept close to normal and protein breakdown is kept at a minimum, with perhaps a little additional protein allowed for building up tissue deficiencies, results in improvement in his condition. Exercise graduated within his growing capacity for it, but never pushed to the point of excessive fatigue, seems of value in restoring his feeling of well being.

It may not be amiss to note that in the opinion of the writer, the phrase "insulin edema," recently encountered, is a misnomer, as it relates to a condition possible of attainment under certain conditions in patients on dietetic treatment alone. Further, we have yet to see the edema of a diabetic which would not disappear with salt and water restriction. If insulin is necessary for treatment, patients should not have it discontinued because of the development of edema.

INFLUENCE OF AGE

All patients using insulin do not receive equal benefit from its use. In part this is dependent on the severity of the disease and on various complicating factors, but there is also an influence which seems most directly related to the age of the patient. The most satisfactory results are obtained in young adults, the middle aged severe diabetics, and children over ten years. The aged patient generally shows a much less rapid recovery of strength, gains weight more slowly, and he requires a proportionately larger dose of insulin to produce a given amount of improvement. Dietetic treatment is more difficult in the young child because of greater liability to gastrointestinal upsets, and a tendency to refuse food. The collection of urine is more

uncertain and blood sugar determinations are more difficult to obtain. Some of the above difficulties are likewise encountered when the patient is treated by dietetic methods alone. When in addition the periodic administration of insulin is required by an aged individual or a very young patient the maintenance of a normal blood sugar level becomes decidedly more difficult.

Aged diabetics also suffer from many complications in part related to their age and also contributed to by the diabetic state. Coldness, numb extremities, muscle cramps, parasthesia, neuritis, ataxia, incoördination, etc., are dependent usually upon permanent organic changes in the circulatory and nervous systems, and the possibilities of improvement under insulin are rather remote.

INSULIN IN CONDITIONS OTHER THAN DIABETES

Woodyatt (46) suggests the use of insulin as an aid for differentiating glycosurias of diabetic origin from that of renal origin or arising from other causes. In the renal cases where the glycosuria is small but continuous irrespective of diet, we have found, in agreement with Woodyatt, that if the blood sugar level is low insulin in doses several times as great as should stop the glycosuria has no appreciable effect. Fletcher has found that the hyperglycemia of arthritis responds to insulin. Of more purely physiological interest is the observation of Hepburn and Campbell that the hyperglycemia and slight glycosuria of carbon monoxide poisoning in man is promptly controlled by insulin. This effect of insulin was previously observed by Banting, Best, Collip, Macleod and Noble (58) working on rabbits.

The use of insulin in the pernicious vomiting of pregnancy is, in our experience, unnecessary. No case of post-operative acidosis has required it and it is difficult to see what purpose it could serve unless it replaces insulin not produced by the pancreas of a patient subjected to excessively long etherization or assists in restoring the glycogen to the liver of the patient subjected to pre-operative starvation as was formerly the practice. Its use in the non-ketonic acidoses is more questionable, and indeed one may be permitted to doubt its value in conditions other than those in which there is a distinct deficiency of endogenous insulin production.

INSULIN IN DIABETES IN PREGNANCY

Diabetes in pregnancy presents a peculiar problem. In many cases not one but two metabolic defects exist: one, the diabetic condition, and the other a very marked disturbance of the ketogenic-antiketogenic ratio consequent upon the damage produced in the liver by pregnancy. In all normal pregnancies there is a deficiency of available base and a reduced alveolar CO_2 tension, indicating a liability to acidosis from non-ketogenic substances and, in addition, there is inability to use as much fat, relative to total glucose, as in the non-pregnant state. As a rule, when these patients are on an ordinary mixed diet or one that is relatively high in carbohydrate the ketogenic substances, since they are formed in but small amounts, do not contribute much to the acidosis. In a proportion of cases, however, more severe liver damage exists and considerable amounts of acetone bodies appear in the blood and the urine. Harding, in Toronto, has shown that most of these cases can be controlled satisfactorily by administering glucose and an adequate amount of fluids. Thalheimer (99) suggested the use of insulin in addition to glucose to control the condition in severe cases. In Toronto no case of uncomplicated pernicious vomiting sufficiently severe to warrant the trial of insulin in addition to fluids and glucose has been encountered in the last three years though we intend to try it for its glycogen storing effect on the liver if a suitable case occurs.

Pregnancy in diabetics, or the development of true diabetes mellitus during pregnancy is especially prone to be accompanied by liver damage with resultant failure to burn completely the acetone bodies and, probably, also a relative inability to produce glycogen when the carbohydrate is imperfectly metabolized. Particular care is necessary to avoid acidosis in these cases and when it becomes established the acidosis is decidedly more difficult to control—marked nausea and vomiting being prominent symptoms. Since pregnancy during diabetes tends, as a rule, to increase the severity of the patient's diabetic condition both during and, usually, after the pregnancy it is inadvisable for the diabetic to become pregnant. The high mortality of the fetus and young infant also renders childbearing in diabetes

hardly worth the risk to the patient. Once established, however, the question often arises as to whether the pregnancy should be terminated or not. Joslin (81) seems to feel that it should not, and I would agree with him so long as it does not involve undue risk to the mother. In some cases induced labor a short time before term, particularly in primiparae, seems to me justifiable, as in well conducted institutions it has little influence on the fetal mortality and saves the mother a prolonged parturition during which she is particularly liable to develop acidosis. Lactation should be avoided since it is a severe drain on the maternal metabolism.

The dietetic treatment in the pregnant diabetic is complicated by the necessity of using a larger relative proportion of glucose to fatty acid so as to avoid acidosis. This should be instituted at the outset of treatment and if the insulin production of the patient is insufficient to maintain an aglycosuric state, with a normal fasting blood sugar, more insulin should be supplied artificially. The total glucose of the diet in grams should at least equal the fat. The protein allowance should not be excessive—1 to 1.25 grams per kilogram of body weight is sufficient. The total energy of the diet should be maintained comparatively lower than in the nonpregnant woman and the patient, as is usual during pregnancy, should be taught to rest as much as possible. In many pregnant diabetics such a plan of treatment is necessary to avoid acidosis, the symptoms of which very much resemble and are, at the same time, more serious than the pernicious vomiting of pregnancy. Insulin will be found necessary to carry out this program, and it should be noted that following parturition some patients may with advantage revert to a diet somewhat higher in fat and lower in total glucose with omission or reduction of the dose of insulin used.

Notwithstanding the use of treatment ordinarily effective, or perhaps because severe acidosis is already present when the patient is first seen, the condition of the patient may become progressively worse. With continued vomiting, loss of food and fluid, the patient grows steadily weaker and more dehydrated. Such patients exhibit a most distressing and dangerous degree of acidosis and may readily lapse into coma. Insulin should be pushed, remembering that time lost in the treatment of such cases cannot be made up later by larger

dosage of the drug. Insulin used immediately will control the acidosis but if this is very severe and vomiting cannot be checked it may be inferred that severe liver damage has been done and that the condition will readily recur. In the more severe cases it becomes obviously impossible to carry the patient to term on an emergency basis. Sometimes such a condition is coincident with the death of the fetus and evacuation of the uterus is necessary. In others abortion is the only recourse. As the liver very soon after this operation is performed becomes capable of again metabolizing the fats the prospects of the mother are fairly good. Professor Hendry informs me that, in his opinion, labor is more safely induced by bougies than by other methods in these severely emaciated, dehydrated patients. In the meantime, however, the physician may have considerable difficulty controlling the patient's acidosis on account of failure to retain an amount of carbohydrate sufficient to prevent insulin hypoglycemia. Rectal injections of 5 per cent glucose solution either in small repeated doses or by the Murphy drip method are useful. A solution of 5 per cent soda bicarbonate may also be administered in the same way. Normal saline may be injected subcutaneously to replace fluid lost, or, if necessary, saline or glucose may be given intravenously. The usual precautions in treating severe acidosis or coma should be carried out.

INSULIN IN INFECTIONS

In our experience the incidence of infections in patients suffering from severe diabetes has decreased when insulin is employed in their treatment, and when infections occur in these patients healing proceeds as in non-diabetic patients. Joslin's (81) experience has been similar. A comparison of diabetics treated in the medical and surgical wards of a hospital shows much more favorable results in the former, due to the greater attention paid to proper dietetic treatment. The patient with a surgical infection is a much greater burden to carry from the medical standpoint than any other type of diabetic, even including the coma cases. In many cases that are badly infected or are in such a state of acidosis that surgical operations cannot be undertaken, it has been found that the institution of suitable dietetic treatment with insulin has resulted either in healing of the infection or in

such a marked improvement in the general condition that any necessary surgical interference could be undertaken with relative safety. In this connection attention may be drawn to the remarkably good results which are often attained by the application of physical therapeutic agents, warmth, radiant heat, diathermy, x-ray, ultra violet ray, etc., in suitable cases.

Infection undoubtedly increases acidosis and reduces the tolerance for carbohydrate. Pus, wherever found, should have free drainage at the earliest possible moment. In preparing a patient for immediate operation it is advisable to neglect glycosuria and concentrate attention on the acidosis for the time. The patient with glycogen in his liver is a much better risk from the standpoint of acidosis and, for this reason, he should be given sugar or other easily available carbohydrate along with insulin. Though diabetics with infection stand enormous quantities of insulin without bad results, it is preferable to use it in the proportion of one unit for each gram of sugar given. If the condition constitute a surgical emergency there should be no delay beyond that necessary for the ingestion of the soluble carbohydrate and the injection of the insulin. The anesthetics of choice are novocaine for intrathecal anesthesia, or paravertebral nerve blocking in suitable cases, or nitrous oxide oxygen by inhalation. Ether should be used sparingly, if at all; chloroform never. The former lowers carbohydrate tolerance temporarily and sometimes permanently while the latter is apt to result in a permanent loss of tolerance and very often coma. Local infiltration may sometimes be used but with caution, as gross damage to tissues is especially to be avoided in patients suffering from diabetes. In many less acute cases surgical interference does not demand other than the routine dietetic treatment. Simple drainage operations under nitrous oxide oxygen anesthesia may be undertaken with comparative safety. The patient, after operation, should be treated as a case of acidosis and gradually allowed suitable foods with enough insulin to abolish glycosuria and reduce hyperglycemia.

Diabetic patients suffering from pneumonia, tonsillitis, bronchitis, etc., should be given 400 to 600 calories more than the basal caloric requirement, with somewhat higher percentage of carbohydrate and

protein than would ordinarily be used in treating the diabetic condition. The meals should be small, as attractive as possible and more frequently served. Foods high in carbohydrate content are used with advantage. Many investigators find it difficult to keep such patients aglycosuric because of the wide variations in tolerance exhibited from day to day. Strouse and Schultz (100) found in a series of five cases with various infections that a slight glycosuria persisted. We have previously noted the markedly increased tolerance to insulin during infections and suggest the use of larger doses of insulin in the treatment thereof. While admittedly more difficult to accomplish in these cases, it is believed that the greatest care should be taken to keep the blood sugar as near the normal as possible.

Dr. F. F. Tisdall has made some as yet uncompleted blood sugar studies on infants the subject of various infections, especially diarrheas, in which he has shown that the rise in the blood sugar curve following the intravenous injection of suitable quantities of glucose is extreme, that the period of high blood sugar is excessively prolonged over the normal and that the injection of insulin is less effective in controlling the hyperglycemia than in the normal. Whether this is associated with deficient function of the islet cells of the pancreas or, as seems possible, is related to the much increased tolerance for administered insulin in adult diabetics, the subject of intercurrent infection is still uncertain.

The use of insulin in tuberculous diabetics has been discussed by several observers (101, 102). The usual effects of the drug are manifested in this disease. Its use, however, permits the administration of a larger caloric intake, so that the increased body nutrition assists in combating the spread of the pulmonary lesion. Insulin probably has no specific effect beyond this. Sansum believes that the tuberculous diabetic treated with insulin has the same opportunity for recovery as the non-diabetic patient suffering from this disease. Among our cases no cures have been observed as yet but several patients show astonishing degrees of recovery.

Since the discovery of insulin very great advances have been made in our knowledge of diabetes. The prognosis of the well-treated diabetic today as compared with his prognosis two years ago is very much

improved. It should be remembered, however, that insulin is not a substitute for dietetic treatment of diabetes. On the contrary, the patient receiving insulin treatment is required to observe the limitations of his disease and of his diet more closely than a patient treated by dietetic means alone, and it is, therefore, not to be employed unnecessarily. However, should a patient respond favorably to dietetic treatment the very existence of insulin has a profound psychic influence upon him. He is aware that there is now a barrier between himself and death in coma if, for any reason, his tolerance should fail, infections occur, or any surgical emergency arise. Secure in this knowledge that he has to reckon with but little more than the usual hazards of life and death, his viewpoint on life has entirely changed. He no longer is depressed; he need no longer spend his days carefully tending the vital spark, but is enabled to enjoy life and work in a more normal manner than heretofore.

When properly employed, insulin largely replaces the lost hormone of the diabetic pancreas, restoring the power to metabolize sufficient food, and makes it possible to treat patients in whom dietetic measures have failed. Despite the attendant disadvantages and inconveniences, insulin means life itself to these unfortunate patients hitherto condemned to a short precarious existence haunted by the imminent presence of death. The mental relief obtained is not less striking than the restored ability to work and to play now possible under insulin treatment.

For the treatment of the patient in acidosis or in coma, notwithstanding the benefits derived from other adjuvants in the treatment of the former and the occasional success of these methods in the latter, insulin has already become the most efficient weapon in the hands of those skilled in its use. Carefully controlled it must be; life-saving it undoubtedly is.

Physicians charged with the prolonged care of patients suffering from diabetes, rather than the treatment of the disease itself, have long since realized the difference between the diabetic to-day and the same patient two years ago. They recognize that the extra initial effort in treating and training patients is more than amply com-

pensated by the increased health and strength of the patients and the simplicity of their subsequent guidance.

Our present knowledge of insulin only reveals more clearly further problems to be solved. Interesting in its history, fundamental in the recent advances in the physiology of metabolism, and of primary importance in the treatment of severe diabetes mellitus, many possibilities of insulin still lie in the future.

CHAPTER XVI

Recipes, Tables of Food Equivalents; Food Analyses[1]

While in general it is advisable for the diabetic to avoid departing too far from the staple articles of food used by the family, a certain amount of extra time and trouble spent in the preparation of his diet adds greatly to his comfort and the changes of his prolonged adherence to adequate dietetic treatment. The adequately treated diabetic is an economic asset; the poorly treated diabetic is a liability. Miss Mame Porter, B.Sc., Dietitian, Toronto General Hospital, has kindly consented to the reprinting of her collection of recipes. I have also to thank my assistant, Miss M. I. Hanna, B.A., for many analyses of foodstuffs and prepared foods not elsewhere available.

RECIPES

Teaspoon = tsp.	3 tsp. = 1 tb.
Tablespoon = tb.	16 tb. = 1 c.
Cup = c.	4 c. = 1 qt.
f.g. = few grains	

30 grams = 1 oz.
15 grams = ½ oz. or 1 tb. liquid

To wash bran

Buy ordinary feed bran. Sift to rid of free starch. Fill a cotton sack about ⅓ full, tie firmly at the top, wash in a vessel of water, changing frequently or leave under running water, turning and kneading. Wash till water comes quite clear of all starchy appearance. Wring as dry as possible. Remove from bag by handfuls, squeezing thoroughly.

Bran may be then either made into wafers, using Recipe I, or dried in a low oven, stirring occasionally.

Thoroughly dried bran may be stored or used as in Recipe II.

[1] Derived principally from Atwater and Bryant: Bull. 28, U. S. Dept. Agriculture. Reprinted by permission from Campbell and Porter, "Notes for Diabetics."

Bran wafers I

6 cups unwashed bran
½ tb. salt
5 tb. India gum
Hot water
1 tablespoon each of cinnamon and nutmeg, and 1 grain saccharine may be added.

Method. Wash bran and prepare as above. Make sauce of India gum with just enough water to make a stiff paste and beat until free of lumps. Combine with remaining ingredients and knead until mixture is smooth. Spread in thin layers on baking sheets greased with mineral oil. Cut in squares. Bake in a slow oven until crisp.

No food value.

Bran wafers II

6 cups dry washed bran
6 tb. India gum
2 tsp. salt
Hot water
1 tablespoon each of cinnamon and nutmeg, and 1 grain saccharine may be added if desired.

Method. Mix dry ingredients thoroughly; add hot water to make a soft dough. Spread in thin layers on a baking sheet greased with mineral oil. Cut in squares. Bake in a slow oven until dry and crisp.

No food value.

Bran muffins

½ c. dry washed bran
2½ tb. Cellu flour
⅓ tsp. baking powder
f.g. salt
⅓ egg
½ tb. India gum
1½ tb. mineral oil
Saccharine if desired

Method. Mix dry ingredients thoroughly; add mineral oil, egg and sufficient warm water to make a batter that will drop from the spoon. Bake in small muffin tins in a slow oven till dry.

Food value: P. 2; F. 2.

Cellu bran wafers

3 c. dry washed bran
1½ c. Celluflour
3 tb. India gum
3 tsp. baking powder
4 tb. mineral oil
2 grains saccharine
Hot water

Method. Mix dry ingredients thoroughly. Add mineral oil and finish as for bran wafers, may be spread somewhat thicker—$\frac{3}{8}$ inch. These may be spiced, flavored with caraway seeds, or nuts may be put in, providing, of course, their food value is calculated.

No food value.

Cellu pie crust

$\frac{1}{4}$ c. Cellu flour	f.g. Salt
2 tb. dry washed bran	Saccharine
2 tsp. India gum	$\frac{1}{2}$ tb. mineral oil
$1\frac{1}{2}$ tb. warm water	

Method. Mix as for Cellu bran wafers, adding sufficient warm water to make a dough. Mould in muffin tins. Bake in a slow oven till dry. This recipe makes two pie crusts.

No food value.

Pumpkin pie

80 to 100 grams pumpkin	Spices
salt	Saccharine
cream	Egg

Method. To the amount of pumpkin stated in diet add 1 tb. cream, from day's allowance, and the white or the yolk of an egg may be added. Season with salt, spices and saccharine. Pour into a crust and bake. Any fruit in diet may be used in place of pumpkin.

Food value with egg yolk: P. 2; F. 6.

Food value with egg white: P. 4.

Diaprotein bread

1 measure diaprotein flour	2 eggs
f.g. salt	2 tb. water

Method. Beat egg yolks till quite thick; add water and fold into stiffly beaten white of egg; then add carefully the flour. Do not stir or beat. Bake in a moderate oven increasing the heat at the last. Loaf must have a firm crust on it or it will lose its shape. Average weight of loaf 140 grams.

Food value, loaf: P. 43.5; F. 13.5.

Food value, 10 grams: P. 3.1; F. 0.9.

Lister flour bread

1 pkg. Lister flour — 3 eggs
f.g. salt

Method. Combine and bake as for diaprotein bread. Average weight of loaf 160 grams.

Food value of loaf: P. 59.9; F. 18.3.

Food value of 10 grams: P. 3.7; F. 1.1.

Soy bean muffin

90 grams soy bean flour — 120 grams buttermilk
2 eggs — 2 tsp. baking powder
¼ tsp. soda — Saccharine

Method. Beat egg yolks and add buttermilk to which soda has been added. Mix other dry ingredients and stir in. Lastly fold in stiffly beaten egg whites. Bake in a moderate oven in muffin tins twenty-five to thirty minutes. Makes 10 muffins.

Food value of 1 muffin: P. 4.9; F. 3; C. 1.6.

Allenbury's bread

1 pkg. Allenbury's flour — 3 eggs
¼ tsp. salt

Method. Combine and bake as for diaprotein bread.

Food value, loaf: P. 57.5; F. 22.1.

Food value, 10 grams: P. 3.6; F. 1.4.

Nutrivoid bread

30 gm. Nutrivoid flour (6½ tb.) — 2 eggs
⅓ tsp. salt

Method. Combine and bake as for diaprotein bread.

Food value, loaf: P. 12.1; F. 12.

Food value, 10 grams: P. 1.5; F. 1.5.

Diabex flour bread

172 grams Diabex flour — ½ yeast cake
⅛ tsp. salt — Warm water

Method. Dissolve yeast cake in 1 tb. luke warm water. Add salt to flour and then add enough water and yeast cake to make a stiff dough, reserving enough dry flour to knead it with. Knead as ordinary bread. Place in small bread pan and bake in a slow to moderate oven for 30 to 40 minutes.

Food value, loaf: P. 24.08; F. 6.88; C. 44.72.

Food value, 10 grams: P. 1.12; F. 0.3; C. 2.08.

Oatmeal porridge

15 grams oatmeal or rolled oats — ¾ c. (scant) hot water

¼ tsp. salt

Method. Weigh amount of oatmeal allowed in diet into saucepan, add salt and then hot water, slowly stirring to prevent lumps. Cook, stirring frequently, till thick. Cook over boiling water two to three hours.

Food value, 15 grams (dry): P. 2.4; F. 1; C. 10.1.

Cheese crackers

Use Cellu bran wafers. Grate cheese about ⅛ thick on them and brown in moderate oven.

Macaroons

1 egg white — 10 grams blanched almonds

¼ grain saccharine, or a few drops of liquid

Method. Beat egg white stiff, fold in the nuts chopped fine; add saccharine. Drop in spoonfuls on waxed paper and brown in a moderate oven.

Food value, P. 6.1; F. 5.4; C. 1.7.

This recipe makes four macaroons. Food value of each: P. 1.5; F. 1.3; C. 0.4. Or 10 grams California walnuts may be used:

Food value: P. 5.8; F. 6.4; C. 1.3.

Food value, each macaroon with nuts: P. 1.4; F. 1.6; C. 0.3.

Peanut cookies

1 egg — 30 grams butter

1 tb. water — 25 grams soy bean flour

Grated rind of 1 lemon — 10 grams chopped peanuts

¼ tsp. baking powder

Method. Hard cook egg; cool and grate. Cream butter and add egg, water and lemon rind, cream well. Add flour and baking powder. Drop in 12 on a baking sheet and bake in a moderate oven, till firm.

Food value of 1: P. 1.5; F. 3.3.

Bran griddle cakes

1 c. dry washed bran
⅓ tsp. salt
½ tsp. baking powder
1 egg
1 tb. fat
¼ c. water

Method. Mix dry ingredients; add water and well beaten egg. Drop in spoonfuls on a hot griddle greased with mineral oil.

Food value: P. 6; F. 18.

If egg and fat are used from diet sheet food value need not be counted.

Cellu griddle cakes

4 tb. Cellu flour
½ tsp. India gum
⅓ tsp. baking powder
1 egg
¼ c. water
f.g. salt

Method. Prepare as in previous recipe.

Food value: P. 6; F. 6.

(May be substitued for 1 egg.)

Maple syrup substitute

2 to 4 grams agar
Saccharine
1 c. hot water
⅓ tsp. Mapleine extract

Method. Dissolve agar by boiling in water. Strain and add saccharine and flavoring.

No food value.

Saccharine syrup

45 grams saccharine powder
⅜ cup cold water

Method. Place in a bottle and leave for three or four days, shaking occasionally.

N.B.: 1 tb. solution equals 2 cups sugar in sweetening power.

Agar syrup

¼ c. agar-agar
2 c. boiling water

Method: Boil till dissolved; strain and add enough hot water to make two cups syrup. This may be used fresh or allowed to cool and set and be re-dissolved over boiling water for thickening cream sauces, gravies, soups, cocoa (made from cocoa shells), etc.

No food value.

Junket

⅓ c. (80 grams) milk
Flavoring
½ junket tablet
1 tb. lukewarm water
Saccharine

Method. Heat milk to blood temperature or 100°F. and pour onto the junket tablet which has been dissolved in water. Flavor, stir well and pour into a mould. Let stand in a warm place till set.

Food value: P. 2.5; F. 3; C. 4.

May serve with bran muffins and have the value of a baked custard.

Baked custard

⅓ c. (80 grams) milk
⅓ egg
Vanilla or nutmeg
f.g salt
⅓ grain saccharine or
a few drops saccharine syrup

Method. Beat the egg and add flavoring, salt and saccharine, and scalded milk. Pour into a custard cup. Place cup in a pan containing hot water and bake in a moderate oven.

Food value: P. 4.5; F. 5.; C. 4.

May treble the recipe: 1 egg and 1 cup milk and make three custards.

Purity custard

1 egg white
f.g. salt
⅓ c. (80 grams) milk
Vanilla or nutmeg
Saccharine

Food value: P. 6.4; F. 3.2; C. 4.

Custard sauce I

⅓ c. (80 grams) milk
⅓ egg yolk
Saccharine
⅓ tsp. flavoring

Method. Combine as for baked custard. Cook in the top of double boiler until mixture coats to the spoon; remove, add saccharine and flavoring.

Food value: P. 3.1; F. 5.2; C. 4.

Served with Bavarian cream or snow pudding. Food value: P. 4.5; F. 5; C. 4.

Custard sauce II

1 egg yolk
20 grams cream, 32 per cent (or 25 grams, 24 per cent)
4 drops saccharine syrup
120 grams milk (½ cup)
½ tsp. vanilla

Method. Pour scalded milk and cream over beaten egg yolk and cook over boiling water till mixture coats the spoon. Strain, cool and flavor. Makes three servings.

Food value, 1: P. 2.1; F. 5.6; C. 2.2.

Served with snow pudding. Food value: P. 4.3; F. 5.6; C. 4.2.

Floating island

⅓ c. (80 grams) milk
⅓ tsp. flavoring
⅓ egg white
⅓ egg yolk
Saccharine

Method. Combine as for custard sauce, reserving egg white. Turn into a mould and pile stiffly beaten egg white on top. Set in the oven to brown. (Or egg white may be folded in as in Spanish cream.)

Food value: P. 4.5; F. 5; C. 4.

Bavarian cream

½ tsp. agar
⅓ c. boiling water
⅓ egg white
½ tsp. lemon juice and grated rind
Saccharine
1 tb. cream (from allowance)

Method. Dissolve agar by boiling in water; strain, add lemon and saccharine; fold in the beaten egg white and the whipped cream, and turn into a cool wet mould. Orange juice or any diabetic flavoring may be used in place of lemon.

Food value: P. 1.3.

Served with milk soup or custard sauce. Food value: P. 4.5; F. 5; C. 4.

N.B.: Bavarian cream may be made without altering food value by folding in 15 grams cream (whip) from allowance just before adding egg white.

Strong coffee may be substituted for fruit juice, adding 60 grams 5 per cent vegetable to allowance.

Orange snow pudding

½ tsp. agar
⅓ c. boiling water
1 tb. orange juice
Grated orange or lemon rind
⅓ egg white

Method. Prepare as for Bavarian cream. May vary recipe by using lemon juice or any diabetic flavoring. Food value: P. 1.3.

Served with milk soup or custard sauce: food value: P. 4.5; F. 5; C. 4.

Snow pudding II

1½ tsp. gran. gelatin.
⅔ cup boiling water
1 egg white
¼ tsp. citric acid powder
⅓ cup cold water
3 tb. orange juice
1 tb. lemon juice
½ lemon rind grated
½ tsp. saccharine syrup

Method. Soak gelatin in cold water. Dissolve in boiling water. Add fruit juice, grated rind, citric acid and saccharine. Strain and put to cool. When beginning to set fold in stiffly beaten egg white and mould at once in three.

Food value of 1: P. 2.2; C. 2.

Served with custard sauce II—food value: P. 4.3; F. 5.6; C. 4.2.

Princess pudding

1 egg yolk
¾ tsp. (1½ gram) gelatin
1 tb. boiling water
2 tsp. lemon juice
2 drops saccharine syrup
1 egg white

Method. Beat yolk till thick; add gelatin dissolved in boiling water and continue beating. Add lemon and saccharine. As mixture begins to thicken fold in stiffly beaten white. Pour into a wet mould.

Food value: P. 7.3; F. 6.6; C. 1.

Spanish cream I

Method. Use the same recipe as for baked custard, reserving egg white and adding ½ tb. agar and ½ c. boiling water (boil till dissolved). Combine as for custard sauce, add the strained agar and continue cooking in the top of double boiler till mixture is thick. Cool slightly; fold in the stiffly beaten white of egg and pour into a cool wet mould.

Food value: P. 4.5; F. 5; C. 4.

Spanish cream II

1 tsp. gran. gelatin
120 grams boiling water
140 grams milk
15 grams cream, 32 per cent (or 20 grams 24 per cent)
2 tb. cold water
1 egg yolk
1 egg white
1 tsp. vanilla or sherry
4 drops saccharine syrup

Method. Soak gelatin in cold water. Dissolve in boiling water. Add to custard sauce made with egg yolk, milk and cream. Strain, flavor and cool. Fold in stiffly beaten egg white and mould at once in three.

Food value of 1: P. 4.2; F. 5.3; C. 2.5.

Served with 60 grams extra 5 per cent vegetable—Food value: P. 4.2; F. 5.3; C. 4.

Coffee cream

½ tsp. gelatin
5 tb. coffee
Saccharine
1 egg
60 grams cream
60 grams hot water

Method. Soak gelatin in coffee; add boiling water, stir till dissolved. Add to beaten egg yolk and cream. Finish as for Spanish Cream. This recipe makes two desserts.

Food value of each P. 4.3; F. 12.6; C. 1.

Gelatin desserts

1 tsp. gelatin
1 tb. cold water
½ c. liquid flavoring
¼ gr. saccharine

Method. May use the allowance of fruit calculated in diet, either as juice or as a fruit with water added, or flavor with diabetic flavoring.

Food value: P. 2.6.

Jelly dessert

1 pkg. D. Zerto
10 grams almonds
½ c. boiling water
20 grams 10 per cent fruit

Method. Pour boiling water over powder and stir till dissolved. Line a mould with fruit and pour jello into it. Set in a cool place till firm. The nuts may be chopped and served over the top with part of the cream allowance whipped, or may be salted, using mineral oil.

Food value: P. 4.1; F. 5.4; C. 3.7.

Jelly whip

Follow recipe for jelly dessert and when jelly begins to set beat and fold in 1 tb. whipped cream, from allowance. Nuts may be served as desired.

Food value: P. 4.1; F. 5.4; C. 3.7.

Cranberry jelly

2 grams gelatin
1 tb. cold water
60 grams cranberries
Saccharine
2 tb. boiling water

Method. Soak gelatin in cold water and dissolve in boiling. Add cranberries which have been cooked and put through a ricer. Turn into a mould and set in a cool place.

Food value: P. 1.8; C. 6.

Agar jelly

2 tb. agar
4 c. boiling water
Saccharine
Flavoring
Coloring

Method. Add boiling water to agar and boil until dissolved. Flavor and color and pour into wet moulds. Grated rind of orange or lemon, or coffee, strained cocoa shells or any diabetic flavoring may be used.

No food value.

Mousse

60 grams (2 oz.) 32 per cent cream
Flavoring
¼ grain saccharine
½ tb. agar-agar syrup

Method. Whip cream, add flavoring, fold in hot agar, put in a covered container and pack in ice and salt 2 to 3 hours. May use any diabetic flavorings, coffee or a part of the day's fruit allowance may be crushed and added to the whipped cream; or serve with a sauce.

Food value: P. 1.4; F. 19.3; C. 2.1.

Orange ice

80 grams orange juice
5 grams lemon juice
2 tb. water
4 drops saccharine syrup

Method. Mix and turn into a tin mould. Pack in ice and salt for two to three hours.

Food value: C. 8.5.

May be substituted for 85 grams 10 per cent fruit during day.

Lemon cream sherbet

60 grams cream 32 per cent (or 75 grams 24 per cent)
2 tb. cold water
4 drops saccharine syrup
f.g. salt
1 tsp. lemon juice

Method. Mix in order given and pack in ice and salt two to three hours.

Food value: P. 1.2; F. 18; C. 2.7.

May be substituted for cream soup by adding 30 grams of 5 per cent vegetable.

Twice cooked apples (10 per cent fruit)

Method. Peel and cut sour apples into eighths; add 1 pint of cold water to each apple, bring to the boiling point. Drain, add cold water and again let boil. Drain and finish cooking in the top of double boiler. May be flavored with a little lemon juice and saccharine. Apples cooked this way may be calculated as 10 per cent fruit.

Prune whip (or any 10 per cent fruit)

40 grams washed prune pulp, 10 per cent
3 drops saccharine syrup
½ tsp. vanilla or sherry
1 egg white
1 tsp. lemon juice
15 grams 32 per cent cream (20 grams 24 per cent)

Method. Cook dried prunes (10 per cent) and wash pulp. Add lemon, saccharine and flavoring. Fold in cream whipped and egg white beaten stiff, reserving enough for a meringue if desired.

Food value: P. 4.3; F. 4.5; C. 4.5.

Waldorf salad

20 grams heart lettuce — 30 grams cubed celery
30 grams raw apple — 2 grams walnuts
Mineral oil mayonnaise

Method. Cube apple into mayonnaise to prevent discoloration; add celery and pile on lettuce. Sprinkle chopped nuts over top.

Food. value: P. 0.3; F. 1.2; C. 6.2.

By omitting 1 gram butter and 60 grams 10 per cent fruit during day this salad will not alter value of diet.

Stewed dried peaches

Soak peaches over night in large amount of cold water. Drain in a colander and return to sauce pan; add water to cover and cook until tender.

Reckon carbohydrate as 7 per cent.

Stewed dried prunes

Split the prunes and remove seeds. Soak over night in large amount of cold water. Drain in a colander and wash in cold water, return to sauce pan, add sufficient water (cold) to cover and cook until tender.

A slice of lemon may be added when cooking.

Reckon carbohydrate as 10 per cent.

Thrice-cooked vegetable 5%

Method. Prepare the vegetables in the usual way. Place in cold water ½ hour. Add fresh cold water and boil 5 minutes. Repeat this three times, the last time cooking until vegetables are tender. Vegetables may be reheated in a little broth or seasoned with meat extracts or vegex. No food value.

Stuffed tomatoes or peppers

Method. Chop fine or grind the allowance of ham, veal or chicken. Add 60 to 80 grams of celery and cabbage, and 20 grams carrots and onion. Season with salt and pepper, mix well, and moisten with broth. Remove top from tomato or pepper, scoop out center, and fill with mixture. Put in pan greased with mineral oil and bake in a hot oven 30 to 40 minutes.

Stuffed carrots

Pick short, thick carrots, scrape and boil till nearly tender. Cool. With a knife scoop out a cavity from one side of carrot. Chop 20 to 30 grams onion, depending on size of carrot. Season with salt, pepper, parsley and vegex or a meat extract may be added. Refill carrot. If butter allowance permits a tsp. may be added (5 grams). Pour over enough clear broth to keep moist. Bake in hot oven 30 minutes.

Beets may be prepared in the same way, using spinach or celery with a little onion to fill cavity.

Food value according to vegetable used.

Fried egg plant

Pare egg plant, cut in thin slices, weigh the amount calculated in diet, sprinkle with salt, weigh and let stand ½ hour. Dredge with cellu flour and fry in mineral oil.

Vegetable cream sauce

1 tsp. agar-agar
2 tb. broth
Seasonings

Method. Dissolve agar in broth, strain and season with salt and pepper and onion juice or chopped parsley may be added. Add ½ to 1 tb. cream from day's allowance.

No food value.

India gum cream sauce

½ tsp. India gum
f.g. salt and pepper
Chopped parsley
3 tb. hot water
few drops onion juice
Cream or milk from allowance

Method. Measure gum into small smooth bottomed bowl and add hot water. Work out all the lumps with a spoon till consistency of a soft jelly. Add cream or milk and seasoning. Heat and serve over fish, meats, or vegetables as desired.

N.B.: Two tsp. gum may be mixed with ¾ cup hot water at a time and mixture used for thickening agent as required (soups, boiled dressings, etc.).

Broth

1 lb. meat and bone
3 c. cold water

Method. Chop meat and bone, soak ½ hour in cold water. Simmer 2 to 3 hours in the same water. Strain, season and serve.

Milk soup

⅓ c. (80 grams) milk
Broth
⅓ egg yolk
5 grams corn or peas

Method. Heat the milk and add to beaten egg yolk. Season with salt, pepper and onion juice. May add ¼ cup broth.

Food value: P. 3.1; F. 5.2; C. 4.

Served in place of broth with Bavarian cream or snow pudding.

Food value: P. 4.5; F. 5; C. 4.

Cream soup

50 grams 5 per cent vegetable or 25 grams 10 per cent vegetable
60 grams 32 per cent cream
Broth

Method. Make a puree of vegetable or chop fine. Season and heat cream and add to hot vegetable. Add sufficient broth to make a serving.

Food value: P. 1.4; F. 19.2; C. 3.6.

Chicken a la king

Chicken
50 to 70 grams mushrooms
⅔ tsp. India gum
10 to 20 grams pimento
60 grams 32 per cent cream
⅔ c. broth

Method. Stew mushrooms in broth till tender, thicken with India gum, add cream and flavor with pimento, salt and pepper. Serve mixture over the amount of hot chicken calculated in diet.

Meat stew

To the amount of cubed or ground round of beef calculated in diet, add ½ c. boiling water and let simmer till almost tender. Then add 80 grams 5 per cent vegetable and 60 grams 10 per cent vegetable and continue cooking till vegetables are tender.

Meat pie

As for meat stew. When cooked turn into casserole and cover with layer of cellu pie crust and bake until crust is dry.

Salmon scallop

Canned salmon
½ tsp. chopped dill pickle
25 grams canned peas
½ tsp. chopped onion
60 grams cream, 32 per cent
Salt and pepper

Method. Weigh amount of salmon allowed in diet in casserole, break up and add seasoning, canned peas and cream. Broth, also, may be added if desired. By omitting cream soup this dish will not alter value of diet.

N.B.: If diet calls for milk soup, milk may be substituted for cream.

Sweetbreads in casserole

Weigh out amount of sweetbreads calculated in diet. Soak in cold water half hour. Parboil twenty minutes. Remove membrane and break apart. Add an equal amount chopped cooked mushrooms. Season and turn into a casserole lined with peas (50 to 60 grams) and 45 to 60 grams cream from day's allowance. Broth may be added if desired.

By substituting vegetables from day's allowance this dish may be used without altering diet.

Cottage cheese I

Put one quart of sour milk in the top of double boiler. Heat this until curb separates out. Let stand for a while. Strain through several thicknesses of cheese cloth and drain till dry. Season with salt and pepper. Chopped pimento and cream from day's allowance may be added.

Cottage cheese II

To one quart buttermilk add slowly 2 quarts boiling water. Let stand until curd separates out. Drain and finish as in cottage cheese I.

Mayonnaise

1 egg
1 tb. mustard
1 tsp. paprika
1 tsp. salt
2 c. mineral oil
2 to 4 tb. vinegar

Method. Beat egg. Add dry ingredients, continue beating, slowly adding oil. When half oil is added, add vinegar and oil alternately. Dressing should be quite stiff when finished.

Food value: P. 6; F. 6. (Negligible when ordinary quantities are used.)

Olive oil may be used instead of mineral oil. Add 9 calories per gram of olive oil used.

Boiled salad dressing

120 grams milk (½ c.)
1 tsp. mustard
¼ tsp. paprika
10 grams butter
1 egg
¼ tsp. salt
1 drop saccharine
2 tb. vinegar (white wine)

Method. Add dry ingredients to egg and beat well. Add scalded milk and cook as custard sauce. When mixture coats spoon remove from fire and add butter and vinegar (slowly); strain, cool and add saccharine.

Food value; 1 tb.: P. 7; F. 1.3; C. 0.4.

By omitting 1 gram butter, 1 tb. may be used without altering diet. If desired add 1 tsp. India gum thickening agent (see cream sauce II).

Salads

For the diabetic who lives away from the city market, where green vegetables are procurable the year round, the finding of something with which to make a salad often becomes a tedious problem.

Cabbage can be had throughout the winter months and readily lends itself to many combinations, may be substituted for lettuce and other salad vegetables.

Cut the stem end from a small firm head of cabbage, place in a bowl of cold water and allow to stand for several hours. The leaves will become fresh and crisp. The inner and more tender ones may be used as you would lettuce or shredded and used as a salad alone or combined with other vegetables such as celery, beets, cucumber, carrots, string beans, etc., or again it may be used as "bed" in which to serve salad foods.

Suggestions for salad combinations

Fruit	*Dressing*
Apple, celery and nuts	Boiled or Mayonnaise dressing
Apple, celery and pineapple	
Grapefruit	
Orange	
Pineapple with cottage cheese balls	Boiled or Mayonnaise dressing
Pineapple, orange and pears (water canned)	
Pear	
Pear half filled with chopped fruit	
Vegetable	
Asparagus	French, Boiled or Mayonnaise dressing
Cabbage, shredded	
Cabbage shredded with celery or nuts	
Sliced tomato	
Sliced tomato with water cress	
Tomato stuffed with celery and cucumber or string beans	
Peas and beets	
Spinach with hard boiled egg	
Cheese	
American or cottage cheese balls with nuts	Boiled, French or Mayonnaise dressing
Celery stuffed with cheese	
Peppers stuffed with ground cheese and celery	
Fish	
Lobster with celery and tomato	French or Mayonnaise dressing
Crabmeat with celery	
Tuna fish with asparagus tips	
Salmon with asparagus tips	
Shrimp with celery	
Tomato stuffed with any of these combinations	
Sardines with shredded cabbage	

Meats

Chicken with celery — Mayonnaise dressing
Turkey with celery
Pepper stuffed with ground ham and celery

The above suggestions are but a few of the numerous combinations which may be made using the 5 and 10 per cent vegetables as a basis.

TABLES OF EQUIVALENTS FOR EGGS, BACON, ROAST BEEF, AND HAM, ETC.

TABLE 11

Equivalents of 1 egg—protein 6, fat 6*

		ADD BUTTER	OMIT BUTTER
		grams	*grams*
1	15 grams bread, Allenbury's	5	
2	15 grams bread, Diaprotein	5	
3	15 grams bread, Lister	5	
4	35 grams bread, Nutrivoid; omit 20 grams vegetable, 5 per cent		
5	20 grams cheese, Canadian or Swiss		1
6	30 grams Cheese, cottage; omit 10 grams fruit, 10 per cent.	7	
7	27 grams cheese, Roquefort		2
8	32 grams cod, salt, boneless with 20 grams 32 per cent cream		
9	40 grams crab meat	6	
10	25 grams finnan haddie, smoked	7	
11	30 grams ham, fried		5
12	30 grams herring, smoked	4	
13	35 grams liver—calf's, raw	5	
14	35 grams mackerel, salt E.P.†		3
15	100 grams oysters—6, omit 100 grams vegetable 5 per cent	5	
16	30 grams salmon, canned	3	
17	25 grams sardines	2	
18	20 grams sturgeon, dried (Russia)	5	
19	20 grams sturgeon caviar, Russian; omit 15 grams fruit, 10 per cent	3	
20	25 grams tuna fish	1	
21	1 Soy muffin and 10 grams extra bacon; omit 15 grams fruit, 10 per cent		

* Take double the weight of equivalent when substituting for two eggs.
† E.P., edible portion; A.P., as purchased.

TABLE 12

Equivalents of 2 eggs and 15 grams cooked bacon—protein 14.2, fat 18

		ADD BUTTER	OMIT BUTTER
		grams	*grams*
1	70 grams cottage cheese; omit 30 grams 10 per cent fruit	21	
2	52 grams cod, salt, boneless	20	
3	One egg and 26 grams bread, Allenbury's, Diaprotein, or Lister	11	
4	1 egg and 45 grams bread, Nutrivoid	5	
5	One egg and 30 grams Canadian or Swiss cheese	1	
6	One egg and 40 grams cottage cheese, omit 15 grams 10 per cent fruit	14	
7	One egg and 40 grams ham, fried		2
8	One egg and 36 grams sardines	5	
9	One egg plus one white and one soy bean muffin; omit 15 grams 10 per cent fruit	11	
10	59 grams finnan haddie	21	
11	65 grams ham fried		4
12	75 grams liver—calf's (raw)	16	
13	77 grams mackerel, fresh (raw)	16	
14	83 grams mackerel, salt, E.P		4
15	51 grams Sturgeon, dried, A.P	16	
16	85 grams sweetbreads, raw	9	

TABLE 13

Equivalents of 2 eggs and 20 grams bacon—protein 15 grams, fat, 20 grams

		ADD BUTTER	OMIT BUTTER
		grams	*grams*
1	75 grams cheese, cottage; omit 30 grams 10 per cent fruit	23	
2	56 grams cod, salt, boneless	22	
3	One egg and 25 grams bread, Allenbury, Diaprotein, or Lister	20	
4	One egg and 50 grams bread, Nutrivoid	7	
5	One egg and 2 soy bean muffins	10	
6	One egg and 35 grams cheese, domestic or Swiss		
7	One egg and 41 grams ham, fried		
8	One egg and 40 grams sardines	7	
9	62 grams finnan haddie	24	
10	70 grams ham, fried		4
11	79 grams liver, calf's	19	
12	79 grams mackerel, fresh	16	
13	87 grams mackerel, salt		3
14	54 grams sturgeon, dried	18	
17	90 grams sweetbreads	11	

TABLE 14

Equivalents of 2 eggs and 25 grams bacon—protein 15.8, fat 22

		ADD BUTTER	OMIT BUTTER
		grams	*grams*
1	75 grams cheese, cottage; omit 30 grams 10 per cent fruit	26	
2	58 grams cod, salt, boneless	26	
3	One egg and 30 grams bread, Allenbury, Diaprotein or Lister	22	
4	One egg and 55 grams bread, Nutrivoid; omit 10 grams 10 per cent fruit	22	
5	One egg and 2 soy bean muffins; omit 20 grams 10 per cent fruit	12	
6	One egg and 35 grams cheese, domestic or Swiss	4	
7	One egg and 45 grams ham, fried	2	
8	One egg and 43 grams sardines	19	
9	66 grams finnan haddie	26	
10	70 grams ham, fried		2
11	83 grams liver, calf's	21	
12	86 grams mackerel, fresh	18	
13	92 grams mackerel, salt		3
14	56 grams sturgeon, dried	20	
15	95 grams sweetbreads	12	

TABLE 15

Equivalents of 2 eggs and 30 grams bacon—protein 16.5, fat 24

		ADD BUTTER	OMIT BUTTER
		grams	*grams*
1	80 grams cheese, cottage; omit 35 grams 10 per cent fruit	28	
2	61 grams cod, salt, boneless	28	
3	One egg and 38 grams bread, Allenbury's Diaprotein or Lister	15	
4	One egg and 55 grams bread, Nutrivoid	12	
5	One egg and 10 grams bacon, 2 soy bean muffins, omit 30 grams 10 per cent fruit		
6	One egg and 37 grams cheese, domestic	5	
7	One egg and 50 grams cheese, cottage; omit 20 grams 10 per cent fruit	21	
8	One egg and 48 grams ham, fried	3	
9	One egg and 45 grams sardines	11	
10	69 grams finnan haddie	28	
11	75 grams ham, fried		1
12	87 grams liver, calf's	23	
13	90 grams mackerel, fresh	21	
14	96 grams mackerel, salt		2
15	59 grams sturgeon, dried	22	
16	100 grams sweetbreads, raw	12	

TABLE 16

Equivalents of 15 grams bacon, cooked—protein 2.2, fat 6

		ADD BUTTER	OMIT BUTTER
		grams	*grams*
1	5 grams bread, Allenbury, Diaprotein or Lister	6	
2	10 grams bread, Nutrivoid	5	
3	10 grams cheese, domestic	3	
4	10 grams cheese, cottage	7	
5	10 grams ham, fried	3	
6	10 grams nuts, almonds; omit 15 grams 10 per cent fruit		
7	10 grams nuts, Brazil		
8	10 grams filberts, hickory nuts; omit 10 grams 10 per cent fruit		
9	20 grams pecans; omit 30 grams 10 per cent fruit		9
10	10 grams sardines	5	

TABLE 17

Equivalents of 20 grams bacon—protein 3, fat 8

		ADD BUTTER	OMIT BUTTER
		grams	*grams*
1	8 grams bread, Allenbury, Diaprotein or Lister		
2	15 grams bread, Nutrivoid	3	
3	10 grams cheese, domestic or swiss	5	
4	15 grams cheese, cottage; omit 20 grams 5 per cent vegetable	8	
5	13 grams ham, fried	4	
6	14 grams nuts, almond; omit 20 grams fruit, 10 per cent		
7	17 grams nuts, Brazil; omit 10 grams fruit, 10 per cent		4
8	20 grams nuts, filberts, hickory; omit 25 grams fruit 10 per cent		6
9	30 grams nuts, pecans; omit 45 grams fruit 10 per cent		15
10	13 grams sardines	6	

TABLE 18

Equivalents of 25 grams bacon, cooked—protein 3.8, fat 10

		ADD BUTTER	OMIT BUTTER
		grams	*grams*
1	10 grams bread, Allenbury, Diaprotein or Lister	10	
2	20 grams bread, Nutrivoid	8	
3	15 grams cheese, domestic or Swiss	5	
4	15 grams cheese, cottage	12	
5	15 grams ham, fried	6	
6	15 grams nuts, almonds, beechnuts; omit 20 grams 10 per cent fruit	2	
7	20 grams Brazil nuts; omit 10 grams 10 per cent fruit		4
8	25 grams nuts, filberts; omit 30 grams 10 per cent fruit		8
9	35 grams nuts, pecans; omit 50 grams 10 per cent fruit		17
10	15 grams sardines	9	

TABLE 19

Equivalents of 30 grams bacon, cooked—protein 4.5, fat 12

		ADD BUTTER	OMIT BUTTER
		grams	*grams*
1	12 grams bread, Allenbury Diaprotein or Lister	12	
2	25 grams bread, Nutrivoid	10	
3	16 grams cheese, domestic or Swiss	7	
4	23 grams cheese, cottage; omit 20 grams 5 per cent vegetable	14	
5	20 grams ham, fried	6	
6	21 grams nuts, almonds, beechnuts; omit 30 grams 10 per cent fruit		
7	26 grams nuts, Brazil; omit 15 grams 10 per cent fruit		6
8	30 grams nuts, filberts; omit 40 grams 10 per cent fruit		9
9	45 grams nuts, pecans; omit 70 grams 10 per cent fruit		23
10	20 grams sardines	9	
11	One soy bean muffin	10	

TABLE 20

Roast beef equivalents

ROAST BEEF	30 GRAMS	35 GRAMS	40 GRAMS	45 GRAMS	50 GRAMS	55 GRAMS	60 GRAMS	65 GRAMS	70 GRAMS	75 GRAMS	80 GRAMS
Beef, boiled	28 + 2*	32 + 3	37 + 3	40 + 4	45 + 4	50 + 5	55 + 5	60 + 5	65 + 5	70 + 6	74 + 6
Beef, round, raw	35 + 4	39 + 5	45 + 6	51 + 7	57 + 8	63 + 8	68 + 9	74 + 10	79 + 11	85 + 11	91 + 12
Beef, round	25 + 8	30 + 9	35 + 10	38 + 11	42 + 12	47 + 14	51 + 15	55 + 16	60 + 17	65 + 18	68 + 20
Beef, sirloin, raw	36 + 2	42 + 3	48 + 3	54 + 3	60 + 3	66 + 4	72 + 4	78 + 4	84 + 5	90 + 5	97 + 5
Beef, sirloin	30 + 6	35 + 7	40 + 8	43 + 10	48 + 11	53 + 12	58 + 13	62 + 14	67 + 15	72 + 16	77 + 17
Chicken, roast, fullgrown	35 + 3	42 + 4	48 + 4	55 + 5	60 + 5	65 + 6	73 + 6	80 + 6	85 + 7	90 + 8	97 + 8
Chicken, roast, young	28 + 8	32 + 10	36 + 11	40 + 12	45 + 14	50 + 15	55 + 16	60 + 18	65 + 19	70 + 21	74 + 22
Lamb chop	30	36 − 1	42 − 1	47 − 2	52 − 2	57 − 2	63 − 2	68 − 2	74 − 2	79 − 3	84 − 3
Lamb chop, raw	35 + 2	41 + 2	47 + 3	53 + 3	59 + 3	65 + 3	71 + 3	76 + 4	83 + 4	88 + 5	93 + 5
Lamb, roast	35 + 5	40 + 5	46 + 6	52 + 7	58 + 8	63 + 8	69 + 9	75 + 10	81 + 11	86 + 11	92 + 12
Mutton, lean	22 + 8	26 + 10	30 + 11	33 + 13	37 + 14	41 + 16	44 + 17	48 + 18	52 + 20	55 + 21	59 + 23
Mutton, roast	26 + 1	31 + 1	35 + 1	39 + 2	44 + 2	49 + 2	53 + 2	57 + 2	62 + 2	66 + 2	71 + 2
Pork chop, lean	27 + 8	31 + 9	35 + 11	40 + 12	44 + 13	49 + 15	53 + 16	57 + 17	62 + 18	66 + 20	71 + 21
Pork, roast, lean	25 + 7	29 + 8	33 + 9	37 + 10	41 + 11	45 + 13	49 + 14	53 + 15	57 + 16	62 + 17	66 + 18
Turkey, roast	25 + 4	29 + 5	33 + 6	37 + 7	41 + 8	45 + 8	50 + 9	54 + 10	58 + 10	62 + 11	67 + 12
Veal cutlet, raw	35 + 7	40 + 8	46 + 9	51 + 11	57 + 12	63 + 13	70 + 14	75 + 15	80 + 16	86 + 17	92 + 18
Veal, roast	25 + 10	29 + 11	33 + 13	37 + 15	41 + 16	45 + 18	49 + 19	53 + 21	57 + 22	62 + 24	67 + 25
Salmon, canned or boiled	35 + 6	40 + 7	46 + 8	51 + 9	57 + 10	63 + 11	70 + 12	75 + 13	80 + 14	86 + 15	92 + 16
Salmon, raw	32 + 2	37 + 3	42 + 3	47 + 3	52 + 4	57 + 4	63 + 4	68 + 4	73 + 5	78 + 5	84 + 5
Trout, lake or salmon, raw	39 + 5	45 + 6	52 + 7	58 + 8	64 + 9	70 + 10	77 + 11	83 + 12	90 + 13	96 + 14	102 + 15
Whitefish, raw	32 + 8	37 + 9	42 + 10	47 + 11	52 + 12	57 + 13	63 + 15	68 + 16	73 + 17	78 + 18	84 + 20
Halibut	33 + 8	38 + 10	44 + 11	49 + 12	55 + 14	60 + 15	66 + 17	70 + 18	77 + 19	82 + 21	88 + 22

* First figure gives the weight of the substitute; second figure the weight of butter required to be added to or subtracted from the day's allowance.

Unless stated all weights are for cooked meats.

TABLE 21

Boiled ham equivalents

BOILED HAM	30 GRAMS	35 GRAMS	40 GRAMS	45 GRAMS	50 GRAMS	55 GRAMS	60 GRAMS	65 GRAMS	70 GRAMS	75 GRAMS	80 GRAMS
Beef, corned	23 + 3*	27 + 3	31 + 4	34 + 4	39 + 4	42 + 5	46 + 5	50 + 6	54 + 6	58 + 7	62 + 7
Beef, roast	26 − 1	30 − 1	35 − 1	39 − 2	43 − 2	48 − 2	52 − 2	56 − 2	61 − 2	65 − 2	70 − 2
Beef, round, raw	30 + 3	35 + 4	40 + 4	45 + 4	50 + 5	55 + 5	60 + 6	65 + 6	70 + 7	75 + 8	80 + 8
Beef, sirloin, raw	32 + 1	37 + 1	42 + 1	47 + 1	53 + 1	58 + 1	63 + 1	68 + 2	74 + 2	79 + 2	85 + 2
Chicken, roast, fullgrown	32 + 2	37 + 2	42 + 3	47 + 3	53 + 3	58 + 3	63 + 4	68 + 4	74 + 4	79 + 5	85 + 5
Chicken, roast, young	24 + 6	28 + 7	32 + 8	36 + 9	40 + 11	44 + 12	48 + 12	52 + 14	56 + 15	60 + 16	64 + 16
Egg c. Domestic Cheese	1	1 c	1 c	1 c	1 c	1 c	1 c	2 c	2 c	2 c	2 c
		5 + 1	8 + 1	10 + 1	15 + 1	18 + 1	20 + 1	5 + 1	8 + 1	10 + 1	15 + 1
Ham, fried	27 − 3	32 − 3	36 − 4	41 − 4	45 − 4	50 − 5	54 − 5	59 − 6	64 − 6	68 − 7	73 − 8
Lamb chop, raw	31 + 1	36 + 1	41 + 1	46 + 1	51 + 1	56 + 1	62 + 1	67 + 2	72 + 2	77 + 2	82 + 2
Lamb, roast	30 + 3	35 + 4	40 + 4	45 + 5	50 + 5	55 + 6	60 + 6	65 + 7	70 + 7	75 + 8	80 + 8
Pork chop, lean	23 + 6	27 + 7	31 + 8	34 + 9	39 + 10	42 + 11	46 + 12	50 + 13	54 + 14	58 + 15	62 + 16
Veal cutlet, raw	30 + 5	35 + 6	40 + 7	45 + 8	50 + 9	55 + 10	60 + 11	65 + 12	70 + 13	75 + 14	80 + 15
Veal, roast	22 + 7	25 + 8	29 + 10	33 + 11	36 + 12	40 + 14	43 + 15	47 + 16	50 + 18	54 + 19	58 + 20
Cod	28 + 8	32 + 9	37 + 10	41 + 11	46 + 13	50 + 14	55 + 16	60 + 17	64 + 18	69 + 19	73 + 20
Halibut, cooked	29 + 6	33 + 8	38 + 9	43 + 10	48 + 10	52 + 11	57 + 12	62 + 13	67 + 14	71 + 15	76 + 16
Lobster	38 + 8	44 + 8	50 + 10	56 + 11	63 + 12	69 + 13	75 + 15	81 + 16	88 + 17	94 + 18	100 + 20
Salmon, boiled or canned	30 + 4	35 + 5	40 + 5	45 + 6	50 + 7	55 + 8	60 + 9	65 + 9	70 + 10	75 + 11	80 + 11
Sardines	26 + 2	30 + 2	35 + 2	39 + 2	43 + 3	48 + 3	52 + 3	56 + 3	61 + 3	65 + 3	69 + 4
Shrimp	24 + 7	28 + 8	32 + 10	36 + 11	40 + 12	44 + 14	48 + 15	52 + 16	56 + 18	60 + 19	64 + 20
Smelts, raw	34 + 7	40 + 8	46 + 9	51 + 11	57 + 12	63 + 13	69 + 14	74 + 15	80 + 16	86 + 18	91 + 19
Trout, lake or salmon, raw	33 + 4	39 + 4	44 + 5	50 + 6	56 + 6	61 + 7	67 + 8	72 + 8	78 + 9	83 + 10	89 + 10

* First figure gives the weight of the substitute; second figure the weight of butter required to be added to or subtracted from the day's allowance.

Unless stated all weights are for cooked meats

TABLE 22

Custard equivalents—Protein 4.5, fat 5, carbohydrate 4

		ADD BUTTER	OMIT BUTTER
		grams	*grams*
1	25 grams almonds		10
2	25 grams Brazil nuts; add 30 grams 7 per cent fruit		14
3	18 grams peanuts		2
4	25 grams California walnuts		13
5	30 grams filberts		17
6	30 grams pecans		19
7	15 grams domestic cheese and 40 grams 10 per cent fruit		
8	One egg white, 15 grams cream and 70 grams pumpkin in custard or pie		
9	15 grams Diaprotein bread and 60 grams 7 per cent fruit	5	
10	15 grams Lister bread and 60 grams 7 per cent fruit	4	
11	15 grams Allenbury's bread and 60 grams 7 per cent fruit	4	
12	One soy bean muffin and 50 grams 7 per cent fruit	3	
13	3 Macaroons and 30 grams 10 per cent fruit or 100 grams rhubarb		
14	3 Peanut cookies and 50 grams 7 per cent (grapefruit)		5
15	One junket and 10 grams almonds; omit 30 grams 10 per cent vegetable		4
16	Bavarian cream or snow pudding II with custard sauce II, and 60 grams 5 per cent vegetable		
17	Floating island		
18	Spanish cream or Spanish cream II and 60 grams 5 per cent vegetable		
19	Coffee cream and 30 grams 10 per cent fruit		9
20	One jelly dessert or jelly whip		
21	Prune whip		
22	15 grams domestic cheese and cranberry jelly; omit 30 grams 10 per cent vegetable		
23	120 grams milk; omit 30 grams 10 per cent vegetable		
24	120 grams buttermilk and 5 grams butter; omit 30 grams 10 per cent vegetable		

TABLE 23

Miscellaneous equivalents

1	May omit 10 grams cottage cheese for 5 grams Lister bread
2	May omit cream soup for mousse with 15 grams of any 10 per cent fruit
3	May omit 30 grams Queen olives for 80 grams vegetable 5 per cent, and 7 grams butter
4	May omit 20 grams Queen olives for 50 grams vegetable 5 per cent and 15 grams cream 32 per cent, or 5 grams butter
5	May omit 100 grams vegetable 5 per cent, for 50 grams vegetable 10 per cent or 30 grams fruit 10 per cent
6	May omit 100 grams vegetable 5 per cent for 10 grams lettuce and 20 grams cubed celery and 20 grams raw apple cubed. 2 grams chopped walnuts may be added and a waldorf salad with mayonnaise served
7	May omit 15 grams oatmeal for 8 grams Lister bread and 100 grams fruit 10 per cent

Amounts of protein, fat and carbohydrate—100 gram portions

TABLE 24

	PROTEIN	FAT	CARBOHYDRATE	CALORIES
Fish				
Bass, black, E.P.,* fresh	20.6	1.7		97.7
Bluefish, E.P., fresh	19.4	1.2		88.4
Clams, long, in shell	8.6	1	2	51.4
Cod, whole, E.P.	16.5	0.4		69.6
Cod, steaks, E.P.	18.7	0.5		79.3
Flounder, E.P.	14.2	0.6		62.2
Haddock, E.P.	17.2	0.3		71.5
Halibut, E.P.	18.6	5.2		121.2
Mackerel, salt, E.P.	18.7	7.1		138.7
Mackerel, Spanish	21.5	9.4		171
Salmon, E.P.	22	12.8		203.2
Smelts, raw	17.6	1.8		87
Pike, grey, E.P.	17.9	0.8		78.8
Whitefish, whole, E.P.	22	7		151
Crabs, hard shell, whole, E.P.	16.6	2	1.2	89.2
Lobster, whole, E.P.	16	1		73
Oyster in shell, E.P.	6.2	1.2	3.7	50.4
Oyster, solids, E.P.	6	1.3	3.3	48.9
Scallops, A.P.	14.8	0.1	3.4	73.7
Shad, whole	18.8	9.6		160.7
Trout, brook, whole	19.2	2.1		95.7
Trout, salmon or lake	18	10		162
Cooked fish				
Cod and haddock	22			88
Bluefish, E.P.	26	4.5		144.5
Halibut, boiled	21	4		120
Mackerel, Spanish, broiled, E.P.	23.7	6.5		155
Salmon, canned or boiled	20	10		170
Sardines	23	20		272
Shrimp, canned	25	1		109
Tunney, canned, E.P.	23.8	20	6	278
Finnan haddie	24.3			97
Smoked and dried fish				
Cod, salt, boneless	27.3	3		112
Herring, smoked, A.P.	20.5	8.8		161
Herring, smoked, E.P.	37	15.8		290
Mackerel, salt	21	22.6		287
Sturgeon, dried, Russian	27.8	18.4		277

* E.P., edible portion; A.P., as purchased.

TABLE 24—*Continued*

	PROTEIN	FAT	CARBOHYDRATE	CALORIES
Meat				
Beef:				
Beef, hindquarter, E.P., med. fat	18.3	21.6		267.6
Beef, sirloin steak, E.P	18.9	18.5		242.1
Beef, tenderloin, A.P	16.2	24.4		284.4
Beef, round, med. fat	20.3	13.6		203.6
Beef, ribs	17.5	24.6		292.6
Beef, sweetbreads, A.P	16.8	12.1		176.1
Beef, shoulder, med. fat, E.P	19.6	11.3		180.1
Beef, tongue E.P	18.9	9.2		158.4
Beef, corned, E.P	26	19		
Beef juice	4.9	0.6		25
Liver	20.4	4.5	1.7	129
Kidney	16.6	4.8	0.4	111.2
Lamb, fresh:				
Lamb, fresh, hind, med. fat.,E.P	19.2	16.5		225.3
Lamb, leg, hind A.P	16	13.6		186
Lamb chops A.P. hindquarter	16.5	16.1		210.9
Lamb chops E.P. hindquarter	19.6	19.1		250.3
Lamb loin no tallow or kidney E.P	18.7	28.3		329.5
Lamb kidney	16.5	8.2		94.8
Lamb, cooked:				
Lamb chop, broiled, E.P	22	30		358
Lamb chop, broiled c̄ bone, A.P	18.4	26.7		313
Lamb, leg, roasted	20	13		216
Lamb, tongue, spiced and cooked, E.P	13.9	17.8		215.8
Mutton, fresh:				
Mutton, fresh, shoulder, med. fat. E.P	17.7	20		250
Mutton, shoulder, lean	19.5	22.9		194.1
Mutton, leg, E.P., hindquarter, med. fat	18.5	18.5		236
Mutton, loin, ā tallow and kidney, E.P	15.5	36.2		387.8
Mutton cooked:				
Mutton, cooked, leg, roast	25	22		302
Mutton, lean, boiled	31	5		169
Mutton chop, lean	22	5		133
Veal:				
Veal, loin chops, med. fat, E.P	20	10		170
Veal, leg cutlets, E.P	20	7		143

TABLE 24—*Continued*

	PROTEIN	FAT	CARBOHYDRATE	CALORIES
Meat—*Continued*				
Veal:—Continued				
Veal, roasting leg, med., fat, E.P.	20.2	9		181.8
Veal, liver	19	5.3		123.7
Veal, roasting shoulder, med. fat., E.P.	19.7	14.4		208.4
Veal, roasting rump, fresh, E.P.	19.8	16.2		225
Veal, cooked:				
Veal, cooked, roast	28	1		121
Beef cooked:				
Beef, roast, E.P.	23	28		344
Beef, boiled	25	23		272
Round steak, fat removed, A.P	27	8		180
Loin steak, sirloin	24	10		186
Loin steak, tenderloin, broiled, E.P	23	10		186
Beef, canned:				
Beef canned, luncheon, A.P	27.6	15.9		255.5
Beef, corned and pickled:				
Brisket	18.3	24.7		295.5
Flank, E.P.	14.6	33		355.4
Plate, E.P.	13.7	41.9		431.9
Rump, E.P.	15.3	23.3		270.9
Corned Beef	2.6	19		275
Tongue, pickled, E.P.	12.8	20.5		235.7
Tongue, canned, whole, A.P.	19.5	23.2		286.8
Tripe, A.P.	11.6	1.2	0.2	58.4
Pork, fresh:				
Chops, lean, A.P.	15.5	14.5		192.5
Chops, lean, E.P.	20.3	19		252.2
Loin, tenderloin, A.P.	18.9	13		192.6
Ham, visible fat largely removed	19.2	16.2		222.6
Liver, A.P.	21	4.5	1.4	131
Pork, cooked, fresh:				
Roast, lean	28	10		202
Chop, lean, cooked	26	6		158

TABLE 24—*Continued*

	PROTEIN	FAT	CARBOHYDRATE	CALORIES
Meat—*Continued*				
Pork, smoked or cured:				
Ham, smoked and boiled	20	22		278
Bacon, med. fat, E.P. raw	9.9	67.4		646.2
Bacon, lean, raw	15.5	42.6		445.4
Bacon, lean, cooked	15	40		420
Poultry:				
Chicken, cooked, capon, E.P	27	11.5		211.5
Chicken broilers, E.P., raw	22	2		96
Chicken, roast, young	25	5		145
Chicken, fullgrown, E.P., cooked	19	16		
Squab	24	10		186
Turkey, roast, E.P	27.8	18.4		276.8
Dairy products				
Butter, A.P	1	85		769
Buttermilk, A.P	3	0.5	4.8	35.7
Cheese, domestic	28	38		454
Cheese, full cream	25.9	33.7	2.4	416.5
Cheese, Neuchatel	18.7	27.4	1.5	327.4
Cheese, Cottage	20		4	96
Cheese, Swiss	27.6	34.9	1.3	429.7
Cream, 16 per cent	2.7	16	3.8	170
Cream, 20 per cent	2.5	21	3.8	214.2
Cream, 24 per cent	2.2	24	3.8	240
Cream, 32 per cent	2	30	3.8	293.2
Cream, 40 per cent	1.8	39	3.8	373.4
Eggs, uncooked, E.P	13.4	10.5		148.1
Egg yolk, cooked	15.7	33.3		362.5
Egg white, cooked	12.3	0.2		51
Milk, whole	3.3	4	5	69.2
Milk, skim	3.4	0.3	5.1	36.7
Nuts				
Almonds, E.P	21	55	15	639
Butternuts, E.P	27.9	61.2	3.5	676.4
Brazil Nuts, E.P	17	67	7	699
Chestnuts, fresh, E.P	6.2	5.4	42.1	241.8

TABLE 24—*Continued*

	PROTEIN	FAT	CARBOHYDRATE	CALORIES
Nuts—*Continued*				
Cocoanuts	5.7	50.6	27.9	589.8
Cocoanuts, prepared, A.P	6.3	57.4	31.5	667.8
Hickory Nuts, E.P	15.4	67.4	11.4	713.8
Peanuts, E.P	26	39	22	543
Peanut Butter	29.3	46.5	17.1	604.1
Pecans, E.P	10	70	15	720
Pignolias	33.9	49.4	6.9	607.8
Walnuts, Calif., E.P	18.4	64.4	13	705.2
Vegetables				
Artichokes	2.6	0.2	16.7	79
Asparagus, fresh, A.P	1.8	0.2	3.3	22.2
Asparagus, canned, A.P	1.5	0.1	2.8	18.1
Beans, Lima, fresh, E.P	7.1	0.7	22.0	122.7
Beans, Lima, canned, E.P	4	0.3	14.6	77.1
Beans, string, fresh, E.P	2.3	0.3	7.4	41.5
Beans, string, canned	1.1	0.1	3.8	20.5
Beets, fresh, E.P	1.6	0.1	9.7	46.1
Beets, cooked, E.P	2.3	0.1	7.4	39.7
Brussel Sprouts, canned	1.5	0.1	3.4	20.5
Cabbage, E.P., large leaf	1.6	0.3	5.6	31.5
Carrots, fresh, E.P	1.1	0.4	9.3	45.2
Cauliflower, E.P	1.8	0.5	4.7	30.5
Celery E.P	1.1	0.1	3.3	18.5
Chickory			15	60
Corn, green, E.P	3.1	1.1	19.7	101.1
Corn, green, canned	2.8	1.2	19	98
Cucumber, E.P	0.8	0.2	3.1	17.4
Egg-plant, E.P	1.2	0.3	5.1	27.9
Endive, fresh, E.P	1		2.6	14.4
Kohl-rabi, E.P	2	0.1	5.5	30.9
Lettuce, E. P	1.2	0.3	2.9	19.1
Lentile, dried	25.7	1	58	347.8
Mushrooms, A.P	3.5	0.4	6.8	44.8
Okra, E. P	1.6	0.2	7.4	37.8
Onions, E. P., raw	1.6	0.3	9.9	48.7
Parsnips, E.P	1.6	0.5	13.8	64.9
Peas, green, E.P	7	0.5	16.9	100.1
Peas, canned	3.6	0.2	9.8	55.4
Peas, dried	24.6	1	62	355.4

TABLE 24—*Continued*

	PROTEIN	FAT	CARBOHYDRATE	CALORIES
Vegetables—*Continued*				
Peppers, green	1.1	0.1	4.6	23.7
Potatoes, A.P	1.8	0.1	14.7	66.9
Potatoes, E.P	2.2	0.1	18.4	83.3
Potatoes, sweet, E.P	1.8	0.8	27.4	124
Potatoes, sweet, A.P	1.4	0.6	21.9	98.6
Pumpkins	1	0.1	5.2	25.7
Pumpkin, canned	0.8	0.2	6.7	31.8
Oyster plant, salsify	1.2	0.1	7	33.7
Radishes, E.P	1.3	0.1	5.8	29.3
Rhubarb, E.P., raw	0.6	0.7	3.6	23.1
Romaine				
Rutabagas	1.3	0.2	8.5	41.2
Sauerkraut	1.7	0.5	3.8	26.5
Soy Beans, fresh, E.P	20	4.3	28	230.7
Spinach, fresh	2.1	0.3	3.2	23.9
Spinach, canned	2.1	4.1	2.6	55.7
Squash, E.P	1.4	0.5	9	46.1
Squash, canned	0.9	0.5	10.5	50.1
Succotash, canned	3.6	1	18.6	97.8
Tomatoes, fresh, A.P	0.9	0.4	3.9	22.8
Tomatoes, canned	1.2	0.2	4	22.6
Turnips, E.P	1.3	0.2	8.1	39.4
Truffles	9.1	0.5	7	68.9
Vegetable marrow	0.1	0.2	2.6	12.6
Watercress	0.7	0.5	3.7	22.1
Fruits, fresh				
Apples, E.P	0.4	0.5	14.2	62.9
Apple, A.P	0.3	0.3	10.8	47.1
Apricots, E.P	1.1		13.4	58
Bananas, yellow	1.3	0.6	22	98.6
Bananas, red	1.2	0.7	17.5	81.1
Blackberries, A.P	1.3	1	10.9	57.8
Cherries, E.P	1	0.8	16.7	78
Cherries, A.P	0.9	0.8	15.9	74.4
Cranberries, A.P	0.4	0.6	9.9	46.6
Currants, fresh, A.P	1.5		12.8	57.2
Figs, fresh, A.P	1.5		18.8	81.2
Gooseberries	1		13.1	56.4
Grapes, A.P	1	1.2	14.4	72.4

TABLE 24—*Continued*

	PROTEIN	FAT	CARBOHYDRATE	CALORIES
Fruits, fresh—*Continued*				
Grapefruit	0.6	0.1	12.2	52.1
Huckleberries, E.P	0.6	0.6	16.6	74.2
Lemon, A.P	0.7	0.5	5.9	30.9
Lemon juice			9.8	39.2
Mangos			13	52
Mulberries	0.3		12.0	49.2
Muskmelons, E.P	0.6		9.3	39.6
Nectarines, E.P	0.6		15.9	66
Oranges	0.8	0.2	11.6	51.4
Oranges, A.P	0.6	0.1	8.5	37.3
Peaches	0.7	0.1	9.4	41.3
Peaches, A.P	0.5	0.1	7.7	33.7
Pears, E.P	0.6	0.5	41.1	53.3
Persimmons, E.P	0.8	0.7	31.5	135.5
Pineapple	0.4	0.3	9.7	43.1
Plums, A.P	0.9		19.1	80
Prunes, A.P	0.7		17.4	72.4
Quince	0.3	0.1	13.1	54
Raspberries, red, A.P	1		12.6	54.4
Raspberries, black, E.P	1.7	1	12.6	66.2
Rhubarb, E.P	0.6	0.7	3.6	23.1
Strawberries, E.P	1	0.6	7.4	39
Watermelon, E.P	0.4	0.2	6.7	30.2
Whortberries, A.P	0.7	3	13.5	59.5
Fruit, canned, preserves, etc.:				
Apple sauce	0.2	0.8	37.2	156.8
Apricots, canned	0.9		17.3	72.8
Blackberries, canned	0.8	2.1	56.4	247.7
Cherries, canned	1.1	0.1	21.1	89.7
Cherries, candied	0.5	0.2	86.6	350.2
Cherries, Mareschino				
Citron, candied	0.1	0.1	78.6	315.7
Figs, stewed	1.2	0.3	40.9	171.1
Ginger-root, candied	0.3	0.2	86.8	350.2
Loganberries	1.1	27.6	11.6	299.2
Olives, green, pickled, A.P	0.8	20.2	8.5	219
Olives, ripe, pickled, E.P	1.7	25.9	4.3	257.1
Olives, ripe, pickled, A.P	1.4	21	3.5	208.6
Orange Marmalade	0.6	0.1	84.5	341.3
Peaches, canned	0.7	0.1	10.8	46.9

TABLE 24—*Continued*

	PROTEIN	FAT	CARBOHYDRATE	CALORIES
Fruits, fresh—*Continued*				
Fruits, canned, preserved, etc.—Continued				
Pears, canned	0.3	0.3	18	75.9
Pineapple, canned	0.4	0.7	36.4	153.5
Prunes, stewed	0.5	0.1	22.3	92.1
Strawberries, stewed	0.7		24	98.8
Fruits, dried:				
Apricots, A.P	4.7	1	62.5	277.8
Banana flour	3.1	0.5	83.4	350.5
Citrons	0.5	1.5	78.1	327.9
Currants, A.P., Sante	2.4	1.7	74.2	321.7
Dates, E.P	2.1	2.8	78.4	347.2
Figs, pulled	4.3	0.3	74.2	316.7
Prunes, E.P	2.1		73.3	301.6
Raisins	2.6	3.3	76.1	344.5
Fruit products:				
Olive Oil		100		900
Raspberry Juice	0.5		49.9	201.6
Unfermented Grapejuice	0.2	0.5	6.9	32.9
Cider Vinegar			0.25	1
Sugar, starches				
Honey, A.P	0.4		81.2	326.4
Molasses Cane, A.P	2.4		69.3	286.8
Cornstarch			90	360
Wheat flour, patent	11.4	1	75	355
Tapioca, A.P	0.4	0.1	88	354
Sago, A.P	9	0.4	78.1	352
Sugar, brown			95	380
Sugar, granulated			100	400
Sugar, maple			82.8	331.2
Syrup, maple			71.4	285.6
Flours:				
Hepco flour	43	21	1	365
Soy bean flour, San Francisco Flour Co	43	16	0.5	318
Allenbury's Diabetic Flour	67	7		331
Diaprotein flour	83	4		368

TABLE 24—*Continued*

	PROTEIN	FAT	CARBOHYDRATE	CALORIES
Sugar, starches—*Continued*				
Flours—Continued				
Gluten flour, Farwell and Rhines, Waterton, N. Y.	46	1.1	43	366
Lister's self rising	68.3	1	9.7	321
Lister's Casein flour	69.9	0.67		286
Nutrivoid flour	5.2	11.3	5.2	143
Soy bean meal, Hancock's	38.8	20.5	11.6	386
Jireh diabetic flour	14	2.2	71.6	322
Patent flour	13.3	1.5	72.7	357
Flour, W.W	13.8	1.9	71.9	360
Cereal and bread:				
Cornflakes	5.5	1.5	81	359.5
Farina, dry	11	1.4	76.3	361.8
Hominy, cooked	2.2	0.2	17.8	81.8
Grapenuts	11.5	0.6	75	351.4
Macaroni, A.P	13.4	0.9	74.1	358.1
Macaroni cooked	3	0.1	15.8	76.1
Oatmeal, dry	16.1	7.2	67.5	399.2
Oatmeal, boiled	2.8	0.5	11.5	61
Puffed Rice	6.7	0.4	80	350.4
Rice, A.P	8	0.3	79	350.7
Rice, boiled	2.8	0.1	24.4	109.7
Rolled Oats, dry	16	7	66.2	397.3
Rolled Oats, cooked	2.8	0.5	11.5	61.7
Shredded wheat	12.1	1.8	75.2	365.4
Bread, white	9		55	
Bread, whole wheat	9.7	0.9	49.7	245.7
Crackers, graham, A.P	10	9.4	73.8	419.8
Saltines, A.P	10.6	12.7	68.5	430.7
Soda crackers, A.P	9.8	9.1	73.1	413.5
Zwiebach	9.8	9.9	73.5	422.3
Miscellaneous				
Chocolate, A.P., bitter	12.9	48.7	30.3	611.1
Chocolate, milk			51	204
Chocolate, sweet			67	268
Cocoa, A.P	21.6	28.9	37.7	497.3
Baking Powder			32	128

TABLE 24—*Concluded*

	PROTEIN	FAT	CARBOHYDRATE	CALORIES
Pickles and condiments				
Cucumber pickles	0.5	0.3	2.7	15.5
Capers	3.2	0.5	5	37.3
Catsup, tomato, A.P.	1.5	0.2	12.3	57
Horseradish	1.4	0.2	10.5	49.4

RULES FOR DIABETICS USING INSULIN

The results of various methods of treatment have a profound influence on the insulin requirement of any patient and also on its efficiency. Sufficient insulin will make any dietetic treatment work for a time. It cannot be too strongly insisted upon that each patient is worthy of the most careful study as an individual case and that he requires careful instruction and training in his own limitations: dietetic requirements, the principles of diabetic dietetics, the properties of insulin and how to administer it, the necessary experience in uranalysis and the symptoms of hypoglycemia and its treatment. No physician should undertake the treatment of considerable numbers of patients without submitting them to a preliminary course of training in a carefully regulated institution.

A memorandum accompanies each bottle of insulin, calling attention to the symptoms of hypoglycemia, its danger and its cure, and also to the method of its administration. Patients should also receive a memorandum in which the essential points in treatment are reviewed. For their convenience the following notes attached to the diet lists are furnished to our patients. Joslin makes use of a similar method for reminding the patient of his necessary limitations.

Information for patients

Weigh all food carefully. Learn to estimate quantity of food accurately in terms of protein, fat and carbohydrate content. Avoid monotony of diet by frequent change in the menu.

Arrange to get adequate rest; over-fatigue and emotional excitement must be avoided.

Careful regulation of the bowels, bathing, cleansing of the teeth, and other hygienic measures should be carried out.

Test the twenty-four hours' urine regularly for sugar and diacetic acid. If sugar appears in the urine reduce diet by one-third. After sugar disappears resume working diet gradually. The appearance of diacetic acid in the urine should be reported to your physician immediately.

Most so-called diabetic foods are dangerous. Refer to your physician before using any such article. Keep a note-book; record your progress and all questions you desire your physician to answer.

Complications, even slight ones such as colds, sore throats, boils, etc., are always serious in the diabetic. If ill from any cause notify your physician; go to bed; keep warm; reduce your diet by one-third; take $\frac{1}{2}$ pint of fluid per hour; take an enema. Coma can be avoided by prompt treatment.

The diabetic should always keep the body weight slightly below the normal.

Read the directions accompanying each bottle of insulin. Be sure your insulin is the proper strength.

Accurate adjustment of diet and insulin dosage is essential for successful treatment. Do not depart from the diet or dose of insulin found suitable unless your physician so advises. Avoid excessive exercise or heavy work.

Hypoglycemia, a condition caused by an overdose of insulin, is serious. Early symptoms are sudden hunger, weakness, fatigue, nervousness, pallor and flushing. The juice of one orange is usually sufficient to control the condition. More severe symptoms are sweating and tremulousness, marked anxiety, apprehension, delirium, unconsciousness or collapse. Lie down and rest. Notify your physician. Take a tablespoonful of corn syrup every ten minutes until relieved. Always have some carbohydrate, such as oranges, corn syrup, candies, or sugar, readily available for such an emergency.

If vomiting or diarrhea occur or a meal is omitted from any cause discontinue insulin. Notify your physician. Do not resume insu-

lin until your physician so advises or you are again able to eat your regular meals.

If your supply of insulin is exhausted decrease the diet by one-third and rest. Resume former diet when fresh insulin arrives.

Remember to sterilize your syringe as instructed before withdrawing the insulin from the bottle and inject the exact amount of solution required into the loose subcutaneous tissue of the body after carefully cleansing the skin with alcohol, ether or tincture of iodine.

Order insulin sufficient for one month. It will not deteriorate. Be sure to order your supply allowing plenty of time for delay in mails.

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